CONTENTS

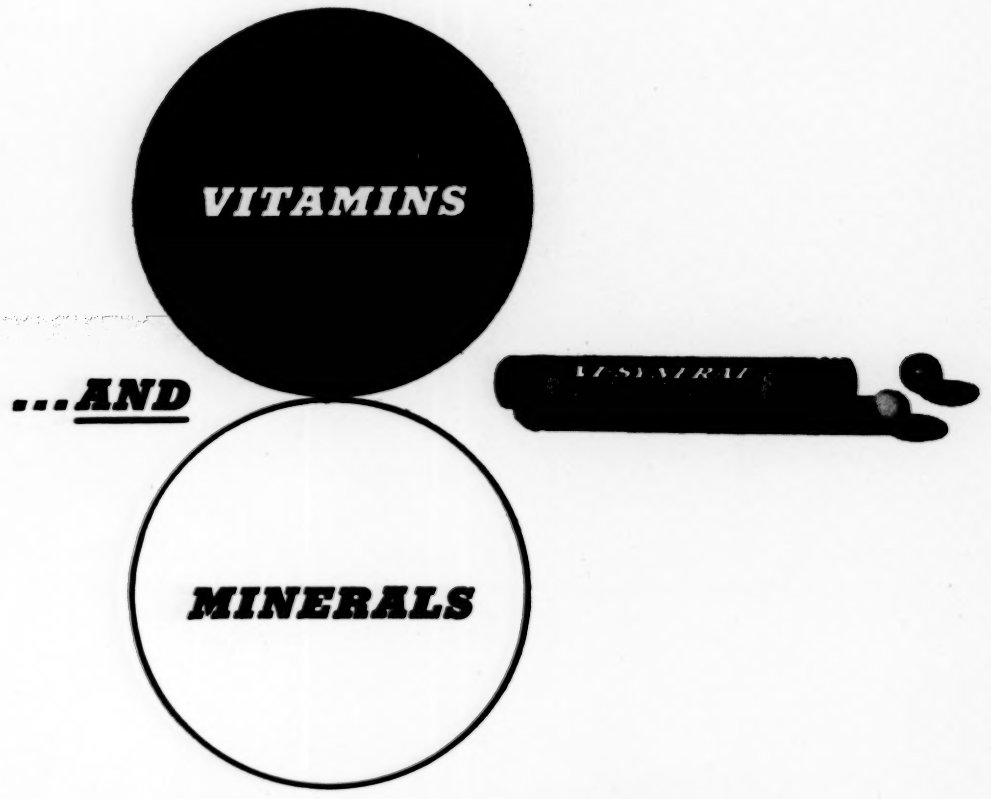
The American Journal of Medicine

VOL. III OCTOBER, 1947 No. 4

Editorial

Clinical Studies

Contents continued on page 5



BECAUSE VITAMINS ALONE ARE NOT ENOUGH

Supplementing the diet with *both* vitamins and minerals is clearly logical because of the now confirmed nutritional concepts originally advanced by Dr. Casimir Funk in 1936:

- vitamins and minerals are nutritionally inter-related
- the same causes produce *both* vitamin and mineral deficiencies (unbalanced diet, pregnancy, etc.)
- minerals are nutritionally as important as vitamins

VI-SYNERAL

IN EACH CAPSULE ...VI-SYNERAL SPECIAL GROUP

Vitamin A (natural)..	12,000 U.S.P. Units
Vitamin D (natural)....	1,200 U.S.P. Units
Thiamine (B_1)	5.0 mg.
Riboflavin (B_2)	3.5 mg.
Niacinamide	20.0 mg.
Pyridoxine (B_6)	2.0 mg.
Calcium Pantothenate	5.0 mg.
Ascorbic Acid (C)	75.0 mg.
Alpha Tocopherol (E)	4.0 mg.
B Complex factors from.....	50 mg. yeast

Phosphorus • Iron • Calcium
Magnesium • Copper • Zinc
Iodine • Manganese

Literature and Samples upon request

U. S. VITAMIN CORPORATION • 250 East 43rd Street, New York 17, N. Y.

CONTENTS

The American Journal of Medicine

VOL. III OCTOBER, 1947 No. 4

Contents continued from page 3

Review

Seminars on Thromboembolism

Conference on Therapy

Clinico-pathologic Conference

Case Report

Special Feature

General Information

THE AMERICAN JOURNAL OF MEDICINE extends an invitation to the profession for original releases on clinical investigations, clinical reviews, case reports and articles designed for postgraduate teaching.

Articles are accepted for publication with the understanding that they are original contributions never previously published. All manuscripts are subject to editorial modification, and upon acceptance become the property of THE AMERICAN JOURNAL OF MEDICINE.

THE AMERICAN JOURNAL OF MEDICINE does not hold itself responsible for any statement made or opinions expressed by any contributor in any article published in its columns.

A reasonable number of illustrations are supplied free of cost; special arrangements must be made with the editor and publishers for excess illustrations and elaborate tables.

Reprints are furnished on order. Prices are quoted on the first day of the month during which article appears. Individual reprints of an article must be obtained from the author.

Material published in THE AMERICAN JOURNAL OF MEDICINE is copyrighted and may not be reproduced without permission of the publishers.

Change of address must reach us by the 15th of the month preceding month of issue.

STATEMENT OF OWNERSHIP

STATEMENT OF THE OWNERSHIP, MANAGEMENT, CIRCULATION, ETC., REQUIRED BY THE ACT OF CONGRESS OF AUGUST 24, 1912, AS AMENDED BY THE ACTS OF MARCH 3, 1933, AND JULY 2, 1946

Of The American Journal of Medicine, published monthly at New York, N. Y., for Oct. 1, 1947.

State of New York } ss.
County of New York }

Before me, a Notary Public in and for the State and county aforesaid, personally appeared S. Minot, who, having been duly sworn according to law, deposes and says that he is the Business Manager of The American Journal of Medicine, and that the following is, to the best of his knowledge and belief, a true statement of the ownership, management (and if a daily, weekly, semiweekly or triweekly newspaper, the circulation), etc., of the aforesaid publication for the date shown in the above caption, required by the act of August 24, 1912, as amended by the acts of March 3, 1933, and July 2, 1946 (section 537, Postal Laws, and Regulations), printed on the reverse of this form, to wit:

1. That the names and addresses of the publisher, editor, managing editor, and business managers are: Publisher, M. T. Wisotzkey, 49 West 45th Street, N. Y. 19, N. Y.; Editor, Dr. A. B. Gutman, 620 West 168th Street, N. Y. 32, N. Y.; Managing editor, P. A. Porter, 49 West 45th Street, N. Y. 19, N. Y.; Business manager, S. Minot, 49 West 45th Street, N. Y. 19, N. Y.

2. That the owner is: The Yorke Publishing Co., Inc., 49 West 45th Street, N. Y. 19, N. Y.; M. T. Wisotzkey, 49 West 45th Street, N. Y. 19, N. Y.

3. That the known bondholders, mortgagees, and other security holders owning or holding 1 per cent or more of total amount of bonds, mortgages, or other securities are: None.

4. That the two paragraphs next above, giving the names of the owners, stockholders, and security holders, if any, contain not only the list of stockholders and security holders as they appear upon the books of the company but also, in cases where the stockholder or security holder appears upon the books of the company as trustee or in any other fiduciary relation, the name of the person or corporation for whom such trustee is acting, is given; also that the said two paragraphs contain statements embracing affiant's full knowledge and belief as to the circumstances and conditions under which stockholders and security holders who do not appear upon the books of the company as trustees, hold stock and securities in a capacity other than that of a bona fide owner; and this affiant has no reason to believe that any other person, association, or corporation has any interest direct or indirect in the said stock, bonds, or other securities than as so stated by him.

5. That the average number of copies of each issue of this publication sold or distributed, through the mails or otherwise, to paid subscribers during the twelve months preceding the date shown above is

(This information is required from daily, weekly, semi-weekly, and triweekly newspapers only.)

S. Minot, Business Mgr.

Sworn to and subscribed before me this second day of September, 1947.

[SEAL] FRANK J. GRIESBECK

(My commission expires March, 1948)

Address all correspondence to

The American Journal of Medicine · 49 West 45th Street · New York 19

Penicillin Oil-and-Wax

Simplest syringe you ever saw!

1. ***Simply attach needle***

No cartridges to insert or change with the Cutter disposable syringe. And note the rubber "knee-action" hilt to absorb shocks and prevent needle snapping.

2. ***Give shot***

That's easy, too. Like your favorite Luer, the Cutter syringe has a pull-back plunger. Lets you aspirate for safety. And Cutter *fluid* P.O.B. is easy to inject in accurately measured doses.

3. ***Then throw the whole syringe away***

Nothing could be simpler! No tricky parts to sterilize or keep track of. Each syringe is a complete unit . . . *completely* disposable.

Cutter P.O.B. simplifies the whole procedure

So fluid, it flows just like salad oil at room temperature. Requires no heating or refrigerating. And, if you use it from vials, there's no struggle to pull *this* penicillin suspension into your own syringe!

You can get Cutter P.O.B. either in handy, disposable syringes or in vials—in 300,000 units, 200,000 units, and 100,000 units per cc. If your pharmacist has none in stock now, ask him to order you a supply.

CUTTER LABORATORIES
BERKELEY 1, CALIF.

Coming!
SYMPOSIUM ON ALLERGY

Guest Editors

ROBERT A. COOKE, M.D., Roosevelt Hospital, *New York*

Francis M. Rackemann, M.D., Massachusetts General Hospital, *Boston*

NOVEMBER 1947

Immunology of Allergic Disease — ROBERT A. COOKE, M.D.

Drug Allergy — WILLIAM B. SHERMAN, M.D.

A Working Classification of Asthma — F. M. RACKEMANN, M.D.

Allergic Dermatitis
CHESTER N. FRAZIER, M.D. and ALLAN A. SMALL, M.D.

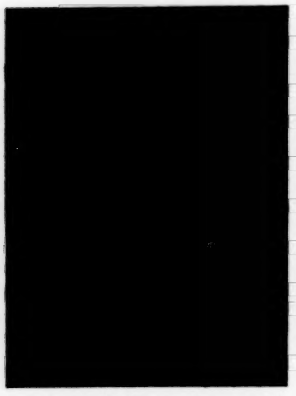
Pharmacology and Therapeutic Effect of Anti-histaminic Drugs
SAMUEL FEINBERG, M.D.

Rôle of Histamine in Anaphylaxis and Allergy
BRAM ROSE, M.D.

Quantitative Immunochemical Aspects of Some Allergic Reactions
ELVIN A. KABAT, M.D.

Classification of the Histologic Reactions in Allergic Diseases
MILTON G. BOHROD, M.D.

Recognition of Emotional Factors in Allergic Manifestations
PAUL A. GLIEBE, M.D. & WILLIAM J. KERR, M.D.



Established July 1946

EDITORIAL BOARD

EDITOR

ALEXANDER B. GUTMAN, M.D.
Assistant Professor of Medicine, Columbia University, College of Physicians and Surgeons, New York

ADVISORY BOARD

WALTER W. PALMER, M.D., *Chairman*
Bard Professor Emeritus of Medicine, Columbia University, College of Physicians and Surgeons, New York
DAVID P. BARR, M.D.
Professor of Medicine, Cornell University Medical College, New York
FRANCIS G. BLAKE, M.D.
Sterling Professor of Medicine, Yale University of Medicine, New Haven
ARTHUR L. BLOOMFIELD, M.D.
Professor of Medicine, School of Medicine, Stanford University, San Francisco
EUGENE A. STEAD, JR., M.D.
Professor of Medicine, School of Medicine, Duke University, Durham,
JOSEPH T. WEARN, M.D.
Professor of Medicine, School of Medicine, Western Reserve University, Cleveland

ASSOCIATE EDITORS

HERRMAN L. BLUMGART, M.D., Boston
HARRY GOLD, M.D., New York
A. McGEHEE HARVEY, M.D., Baltimore
GEORGE H. HOUCK, M.D., San Francisco
CHESTER S. KEEFER, M.D., Boston
T. GRIER MILLER, M.D., Philadelphia
WALTER L. PALMER, M.D., Chicago
OSWALD H. ROBERTSON, M.D., Chicago
EPHRAIM SHORR, M.D., New York
GEORGE W. THORNE, M.D., Boston
WILLIAM S. TILLETT, M.D., New York
ROY H. TURNER, M.D., New Orleans
RUSSELL M. WILDER, M.D., Rochester, Minn.
M. M. WINTROBE, M.D., Salt Lake City
W. BARRY WOOD, M.D., St. Louis
JOHN B. YOUMANS, M.D., Chicago

THE YORKE PUBLISHING CO., INC.
also publishers The American Journal of Surgery

SUBSCRIPTION ORDER FORM

THE AMERICAN JOURNAL OF MEDICINE
49 WEST 45TH STREET, NEW YORK 19, N. Y.

Please enter my subscription to the new monthly journal, THE AMERICAN JOURNAL OF MEDICINE. Subscription U.S.A. $10.00 per year. $12.00 Foreign.

NAME_____ ADDRESS_____

CITY_____ STATE_____

Prompt antacid effect

. . . *sustained relief*

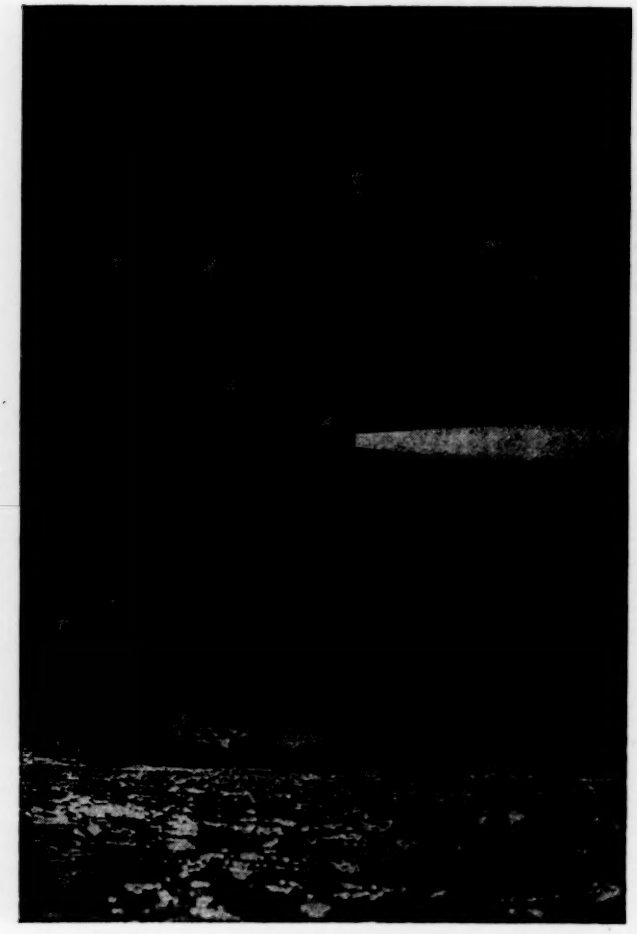
Alminate disintegrates in the stomach in a matter of minutes so that relief is gratifyingly prompt. It is characteristic of Alminate that antacid effect is well sustained so that relief of symptoms is prolonged. A most important advantage is the relative absence of any constipating effect.

Alminate Tablets are appreciated by the patient because they are so convenient to carry and so palatable and easy to take. One or more tablets are swallowed as required; they need not be chewed.

Alminate Bristol is at your own pharmacist's in bottles of 100 and 500 tablets. Complete literature and a test supply on request.

Bristol

LABORATORIES INC. SYRACUSE, NEW YORK



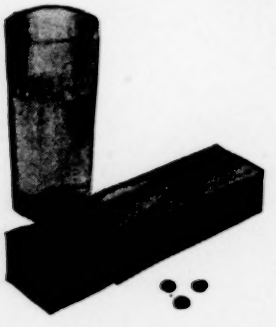
SAFETY

An outstanding characteristic of

MANDELAMINE

Reg. U. S. Pat. Off.

(Methenamine Mandelate)



Mandelamine is supplied in enteric coated tablets of 0.25 Gm. (3¾ grains) each, in packages of 120 tablets, sanitaped, and in bottles of 500 and 1000.

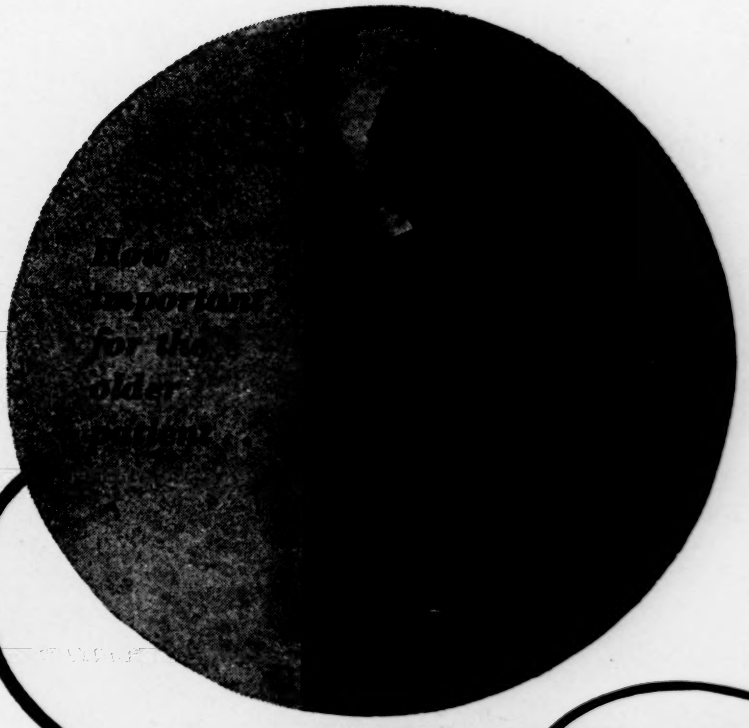
Mandelamine, a highly efficient urinary antiseptic, is virtually nontoxic in effective therapeutic dosage. This remarkable lack of toxicity, as established and confirmed in a number of authoritative clinical studies, facilitates therapy and eliminates the necessity for careful selection of patients. Its safety and ease of therapy make Mandelamine especially suitable for administration to children, during pregnancy, and in stubborn or inoperable cases where therapy is necessarily prolonged. The only major contraindication to Mandelamine therapy is renal insufficiency.

A physician's sample and literature will be sent on request.

NEPERA CHEMICAL COMPANY, INC.

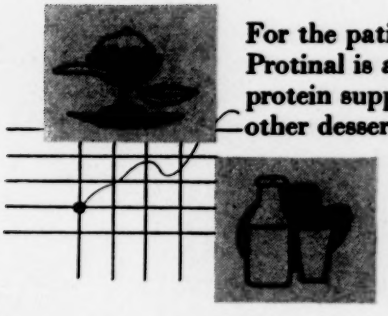
Manufacturing Chemists

Yonkers 2
New York



SODIUM-FREE INTACT PROTEIN THERAPY

In giving the elderly patient supplemental proteins there is no longer a need to accept increased sodium intake in the bargain. Through intensive research, The National Drug Company has succeeded in reducing the sodium in a *complete protein* product down to 0.05 per cent—a negligible amount.



For the patient capable of metabolizing whole proteins, Protinal is a digestible, pleasant-to-taste, concentrated protein supplement. Mixed with a tasty pudding or other dessert, or dissolved in milk, 20 grams with each meal will frequently suffice to bring the patient's protein up to the optimal. The dosage should, of course, be adjusted for each individual.

For sodium-free, complete protein therapy recommend

Protinal is available in bottles of eight ounces and one pound (Chocolate and Plain)

Protinal

A PRODUCT OF MODERN RESEARCH

THE NATIONAL DRUG COMPANY • Philadelphia 44, Pa.

PHARMACEUTICALS, BIOLOGICALS, BIOCHEMICALS FOR THE MEDICAL PROFESSION

SYSTEMIC REHABILITATION

the joy of living restored

Darthronol—an important aid in alleviation of pain—combines the beneficial antiarthritic effects of massive dosage vitamin D with the nutritional and pharmacologic actions of eight other essential vitamins. Darthronol is an important part of the antiarthritic regimen.

An extensive bibliography describing the therapeutic value of each of the nine constituents of Darthronol, together with clinical samples, will be sent on request.

J. B. ROERIG AND COMPANY

ARTHRONOL

for the Arthritic

536 Lake Shore Drive • Chicago 11, Illinois

First lady of the dining room . . . .

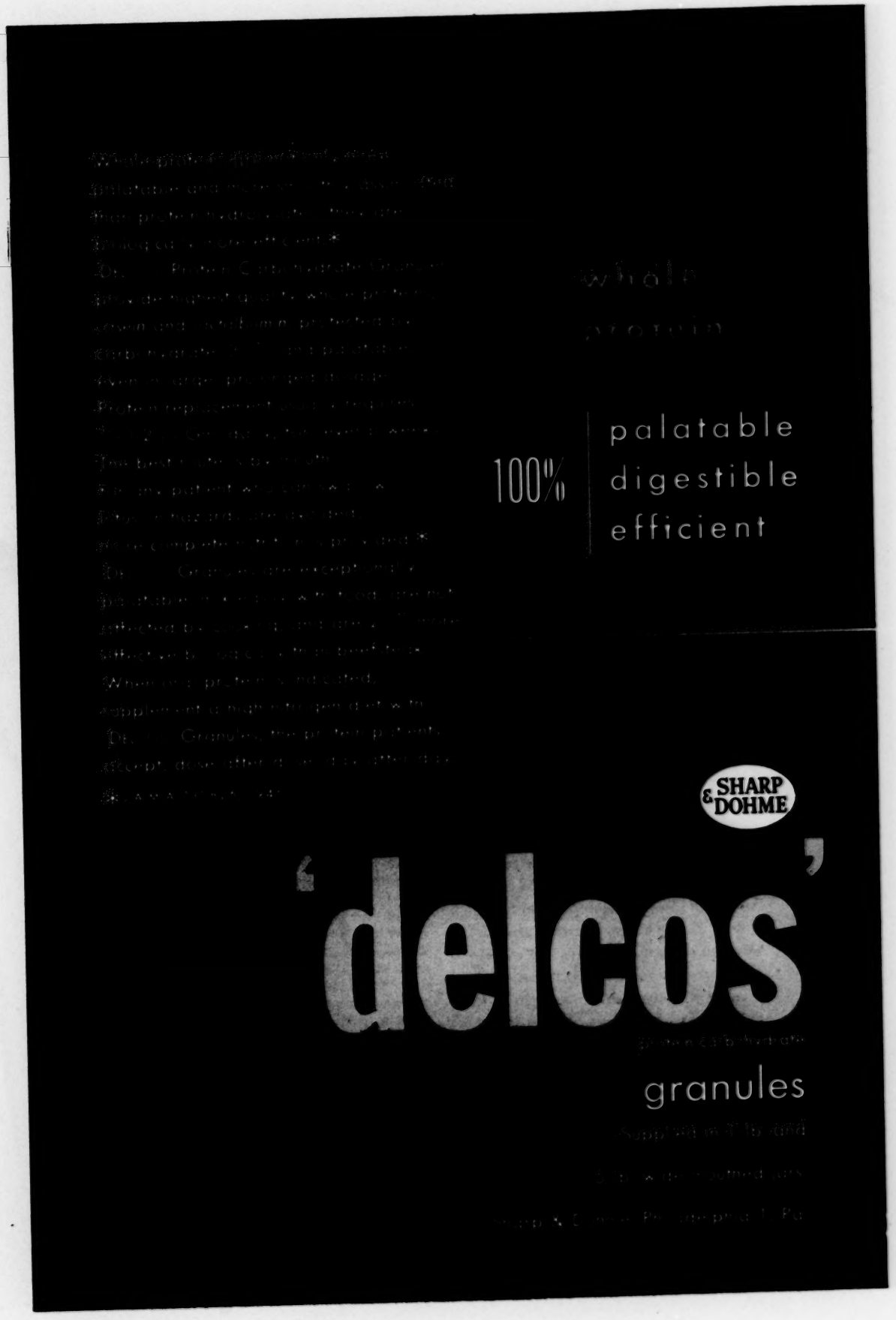
dietary dub!

She beckons the eating public through meal after tempting meal—but, for herself, ignores her own words. And thus she joins the crowded ranks of subclinical vitamin deficiency cases—the people "too busy" to eat properly, those on self-imposed reducing diets, excessive smokers, food faddists and many others. To you, it's the old, old story—and one too common among all economic groups. Since the bodily reserves of the vitamin B complex are not large, even with good diets, many physicians are fortifying the corrected diet with a dependable vitamin B preparation—and very often Sur-bex is the choice. It is a pleasant-tasting, high potency vitamin B complex tablet containing therapeutic amounts of three B complex factors with added liver concentrate and dried brewer's yeast. Sur-bex tablets have a bright, orange-colored double coating which masks all traces of unpleasant odor. Specify Sur-bex, available through prescription pharmacies everywhere in bottles of 100, 500 and 1000 tablets.

Each Tablet Contains:
Thiamine Hydrochloride. 6 mg.
Riboflavin . . . . . 6 mg.
Nicotinamide . . . . . 30 mg.
Pyridoxine Hydrochloride . . . . . 1 mg.
Pantothenic Acid (as calcium pantothenate) . . 10 mg.
Liver Concentrate* . . . . . 0..3 Gm. (5 grs.)
(70% alcohol-insoluble fraction)
Brewer's Yeast Dried* . . . . . 0.15 Gm. (2½ grs.)
*For other B Complex factors.

SUR-BEX®

Abbott ABBOTT LABORATORIES • NORTH CHICAGO, ILL.


whole
protein
100%
palatable
digestible
efficient
SHARP & DOHME
'delcos'
granules

Ulcer Therapy
No. 5 OF A SERIES

Modern Management of Peptic Ulcer

Intragastric Drip Therapy

Intragastric drip therapy with Amphojel® or Phosphaljel,® now an established procedure in the treatment of peptic ulcer, can often be of tremendous value.

The Wyeth intragastric drip apparatus has been placed in more than 1500 hospitals, as a service to physicians and their patients. It provides painless around-the-clock medication at the site of the ulcer—enables the patient to sleep comfortably while the ulcer is being treated. (Complete information on intragastric drip therapy will be gladly mailed upon request.)

For gastrojejunal ulcer Wyeth offers Phosphaljel—a mild and palatable gel of aluminum phosphate. Many physicians prefer Phosphaljel for treatment of all ulcers, or for prophylaxis against seasonal recurrence.

Standard treatment in the modern management of peptic ulcer is based on Amphojel — Alumina Gel, Wyeth. Amphojel provides prompt relief from pain . . . complete security against alkalosis or "acid rebound" . . . nutritional and psychological advantages of a liberal bland diet . . . faster weight gain during treatment. Amphojel is also ideal for the control of gastric hyperacidity not complicated by ulcer.

Other Wyeth specialties valuable in treating peptic ulcer are:

Amphojel without Flavor—for patients who prefer an unflavored preparation.

Amphojel Tablets—for convenience of ambulatory patients.

Amphojel with Magnesium Trisilicate—for ulcer patients with constipation.

Amphojel with Mineral Oil—for ulcer patients with constipation.

Lactamin®—a complete hydrolyzed protein digest supplying all essential amino acids.

WYETH INCORPORATED Wyeth® **PHILADELPHIA 3, PA.**

INTERMEDIATE SEDATIVE
BUTISOL SODIUM

Although prompt in its initial action, Butisol Sodium has not the fleeting, intensified effect of the short-acting barbiturates. Its action has been described as "intermediate." With proper regulation of dosage there is no cumulative action (is destroyed in the body) and a minimum of "hang-over." Butisol Sodium is a valuable sedative for:

DAYTIME SEDATION . . . NEUROSES . . . INSOMNIA
RELIEF OF PREOPERATIVE APPREHENSION
OBSTETRICAL HYPNOSIS . . . MENOPAUSAL HYSTERIA

DOSAGE FORMS: Elixir Butisol Sodium, 0.2 Gm. (3 gr.) per fl. oz.—in pints. Capsules, 0.1 Gm. (1½ gr.) and Tablets, 15 mg. (¼ gr.) and 50 mg. (¾ gr.). Caution: Use only as directed.

Elixir BUTISOL SODIUM

Bright, green color and inviting flavor appeal to all patients; excellent prescription vehicle. Clinical samples available on request.

McNEIL

LABORATORIES, INC. • PHILADELPHIA 32, PA.

Check the B.M.R.

The basal metabolic rate is still the most significant criterion in diagnosing hypothyroidism. And the goal of therapy in hypothyroidism is the restoration and maintenance of a normal B. M. R. To attain this goal a thyroid preparation of dependable, unvarying potency and accurate standardization is essential. To this end, THE ARMOUR LABORATORIES, pioneers in this field, has long led the way in developing new and better methods of preparing medicinal thyroid from the world's largest supply of fresh animal material.

Supplied in 1/10, 1/4, 1/2, 1, 2, and 5 grain tablets and in powder, U. S. P.

℞ Thyroid Armour

Have confidence in the preparation you prescribe . . . specify ARMOUR

THE ARMOUR LABORATORIES

CHICAGO 9, ILLINOIS

Headquarters for Medicinals of Animal Origin

CIBA ANNOUNCEMENT TO DOCTORS

Two new

Ciba Hormone Products

ETHINYL ESTRADIOL is the most potent oral estrogen. Derived from alpha-estradiol, the estrogenic substance secreted by the human graafian follicle. it is free from the comparatively large quantities of non-estrogenic material present in water-soluble urinary derivatives.

In contrast with the synthetic stilbenes, ETHINYL ESTRADIOL brings about a sense of well-being in the menopausal patient and is relatively free from the unpleasant side effects so often produced by the synthetic stilbenes.

Only 0.02 mg. daily will maintain the average menopausal patient; 0.05 mg. three times daily may be required for initial therapy.

ETHINYL ESTRADIOL 0.02 mg.		ETHINYL ESTRADIOL 0.05 mg.	
Bottle of 100 Tablets	$2.10*	Bottle of 100 Tablets	$3.48*
Bottle of 250 Tablets	$4.98*	Bottle of 250 Tablets	$8.16*

LUTOCYLOL® LINGUETS®

LUTOCYLOL LINGUETS provide the most efficient form of administration of the most potent oral progestational substance.

LINGUETS are especially designed to be placed between the gum and cheek where the hormone may be absorbed directly into the systemic circulation. This largely prevents hepatic inactivation so that *LUTOCYLOL LINGUETS are approximately twice as effective as swallowed tablets.*

In threatened abortion, 10 to 30 mg. daily are required for treatment; 10 mg. daily or every other day for maintenance.

LUTOCYLOL LINGUETS 10 mg.	
Box of 30	$ 8.10*
Box of 100	$23.40*

MALE HORMONES REDUCED 35%

In August of this year, the pioneer androgens, PERANDREN® and METANDREN®, were reduced in price 35%. The Ciba policy of passing on the saving made possible by large-scale production of hormones has thus extended the benefits of androgen therapy to many patients to whom they were previously denied.

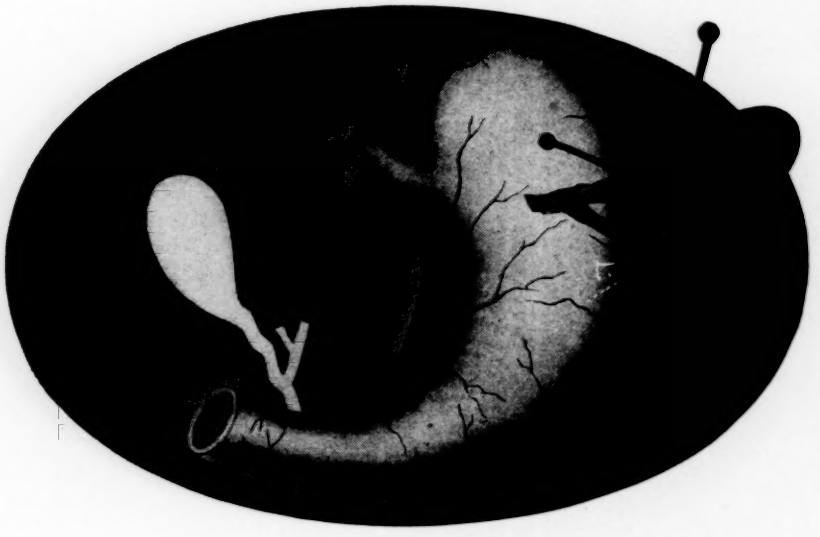
LUTOCYLOL® LINGUETS®—brand of anhydrohydroxyprogesterone
PERANDREN®—brand of testosterone propionate
METANDREN®—brand of methyltestosterone

***PHYSICIANS' LIST PRICES**—*All Ciba products are sold through retail pharmacies. The prices shown are average charges to the physician by druggists, altough they vary in different localities.*

®T.M.Reg.U.S.Pat.Off.

Ciba PHARMACEUTICAL PRODUCTS, Inc., SUMMIT, NEW JERSEY

Bile in the Stomach?



This illustration has purposely been made to show the common duct opening into the stomach. Had nature intended the bile to be excreted in the stomach, she would have placed the opening there herself. Instead, nature releases bile in the small intestine, in which it carries out its function most efficiently.

Pulvules 'Bilron' (Iron Bile Salts, Lilly), like nature, release bile acids in the intestine.
Iron bile salts are made in order to render the natural, conjugated bile acids insoluble in acid media. Hence, 'Bilron' passes through the normal stomach without causing gastric distress.
In the intestine, it readily dissolves at the optimum point for emulsification and absorption of fats.

'Bilron'

ELI LILLY AND COMPANY
Indianapolis 6, Indiana, U. S. A.

The American Journal of Medicine

VOL. III OCTOBER, 1947 No. 4

Editorial

Significance of Psychosomatic Medicine

THE present vogue of psychosomatic medicine is in large part attributable to two rather separate factors. One is the development of methods by which the physical components of emotions may be objectively evaluated, and the other is an increasing realization of the limitations of prevalent scientific procedures in the understanding and management of illness which is dependent upon emotional disturbances. Interest in the subject has been so stimulated that psychosomatic medicine now threatens to become still another specialty in the already alarmingly segmented medical effort.

Although the clinical importance of emotional reactions has long been recognized, preoccupation of physicians with physical and chemical abnormalities in disease has left little time for inquiry concerning their precise effects on the function and structure of the body. It is only in recent years that systematic study has been attempted by methods which permit objective measurement and evaluation. The observations of Wolf and Wolff[1] upon the behavior of the stomach during emotional stress opened the way to a new approach in the field of clinical investigation. They demonstrated that embarrassment and resentment, long known to cause blushing of the face, simultaneously produced flushing, hyperemia and increased acid secretion in the normal stomach and that continuation or frequent repetition of the emotional reaction caused erosions of the gastric mucosa with symptoms which were indistinguishable from those of peptic ulcer. Of equal significance were their observations that in the same individual fear and dread were accompanied by blanching of the gastric mucosa with diminution or a temporarily complete absence of gastric secretion, with loss of appetite and disgust for food. Later studies by Wolff, Holmes, Goodell and Wolf[2] have shown that in the normal nasal mucosa, resentment and embarrassment produce hyperemia and excessive secretion while fear results in pallor and dryness. Observations by Almy and Tulin[3] have shown similar reactions of the normal colon under the stress of pain and emotion.

There is little reason to suppose that the response to emotion of other tissues and organs is less significant. The literature is replete with evidence indicating the participation of the heart, the peripheral circu-

[1] WOLF, STEWART and WOLFF, HAROLD G. Human Gastric Function. New York, 1943. Oxford University Press.

[2] WOLFF, H. G., HOLMES, T. H., GOODELL, H. and WOLF, S. Life situations, emotions and nasal disease. Changes in nasal function associated with varying emotional states and life situations. *Tr. A. Am. Physicians*, 59: 88, 1946.

[3] ALMY, T. P. and TULIN, M. Alterations in colonic function in man under stress. Experimental production of changes simulating the "irritable colon." *Gastroenterology*, 8: 616, 1947.

lation and the kidneys. It is now generally recognized that such diverse conditions as asthma, hypertension, thyrotoxicosis, ulcerative colitis, sinusitis and glaucoma are influenced symptomatically and perhaps etiologically by the play of the emotions.

While these significant observations have been accumulating, experience during the war has greatly emphasized the already growing recognition of the importance of emotional reactions in the development of illness. It has also brought into clearer focus the inadequacy of routine methods of examination and treatment when applied to emotional abnormalities. Actually, in the majority of the military personnel who became ill physical examination and the diagnostic application of x-rays and chemical tests failed to reveal the source of the difficulty. No specifics were available to correct faults of motivation and adjustment. To discerning physicians, the conditions of war appeared to be only an exaggeration of those in civil practice when dependence is placed chiefly on diagnostic and therapeutic procedures which cannot solve all the problems of any patient or any of the problems of many others.

Scrutiny of the rapidly accumulating experience leads to a number of generalizations of clinical significance. Physical concomitants of emotion occur in every human being. Organic disease affords no immunity and usually exaggerates anxieties and fears. Freedom from physical defects and excellent nutrition do not protect the individual from emotional disaster. Indeed, in the evaluation of disease, no diagnosis can be complete, no management optimal which does not take into account the patient's attitude and reaction to his own illness and life situation. In such observations the response of the individual can never be sharply separated into emotional and organic components. In a resentful man the effect of the situation which annoys him will be portrayed in his nose, stomach, posture and the "sour" look on his flushed face. The entire organism reacts to an environment which it regards as threatening. Experience also indicates that while one emotional storm may lead to disagreeable symptoms, frequent repetition of the reaction over considerable periods of time is necessary before simulation of serious organic disease and physical incapacity are likely to result.

Many physicians, perhaps a majority, find themselves unprepared and relatively helpless before a patient in whom no defect can be demonstrated but who persists in being ill. In medical schools emphasis has been placed on the recognition of organic disease or of systemic conditions in which chemical abnormalities can be demonstrated. Deplorably little attention has been given to examination and evaluation of the emotional reactions of the sick man. Under these circumstances, an attitude is gaining ground both in the profession and among the laity that a patient who is ill without recognizable organic defect should seek a psychiatrist. At the same time it is recognized that there are too few psychiatrists and that more cannot be quickly trained. In the dilemma emphasis is being placed upon the necessity of immediate preparation of a group of physicians who will become interested in the interplay of physical and emotional factors and who might be called, for want of a better term, specialists in psychosomatic medicine.

There can be little question as to the desirability of training many men in this field and among them a number who will later be able to act as teachers. Separation of such a group as specialists is less defensible and may actually impede the final solution of the problem. Psychosomatic medicine is medicine itself and cannot be assigned to any one group. The analysis of a patient's reaction to life situations is as much a part of diagno-

sis as is physiology, chemistry or anatomy. Fundamental concepts which pervade understanding of all diseases must never be regarded as clinical specialties. Eventual solution of the practical problems of psychosomatic medicine must rest upon an appropriate orientation of all young physicians and will depend upon broad changes in medical curricula and hospital disciplines, if it is to acquaint them from their earliest day with the physical and emotional responses of human beings under the stress of life situations.

DAVID P. BARR, M.D.

Clinical Studies

Primary Hypertrophy and Hyperplasia of the Parathyroid Glands as a Cause of Hyperparathyroidism*

H. Milton Rogers, M.D. *and* F. Raymond Keating, Jr., M.D.
ROCHESTER, MINNESOTA

Primary hyperparathyroidism is usually caused by a hyperfunctioning neoplastic tumor limited to one parathyroid gland or sometimes involving two. Occasionally, hyperparathyroidism is caused by enlargement of parathyroid tissue resulting from a remarkable primary hypertrophy and hyperplasia of water-clear cells. Albright, Bloomberg, Castleman and Churchill[1] in 1934, were the first to call attention to the clinical and surgical significance of this lesion. They described enlargement of all four parathyroid glands which was considered by them to represent hyperplasia. This enlargement was accompanied by a distinctive histologic appearance and characterized by uniformity of structure, enormous size of the cells, extreme clearness of the cytoplasm and a tendency toward glandular formation.

It is the purpose of this report to review the published cases of primary hypertrophy and hyperplasia of the parathyroid glands and to summarize the findings in four patients seen at the Mayo Clinic. Castleman and Mallory[2] in a comprehensive review of the pathology of hyperparathyroidism found 160 cases of hyperfunctioning lesions of the parathyroids in the literature. In twenty-five of these patients the histologic examination of the lesion disclosed only "wasserhelle" cells. In eleven patients, however, the lesion involved only one gland; therefore, these were considered to be cases of wasserhelle adenoma or neoplasia. In the remaining fourteen patients all parathyroid tissue was involved and the condition was regarded as wasserhelle hyperplasia. In one case the lesion, classified by Castleman and Mallory (Case 112) as an adenoma, fulfills the requirements of wasserhelle hyperplasia. They added five patients seen at the Massachusetts General Hospital, which brought the total recorded instances of primary hyperplasia of the parathyroid glands up to twenty.

In our review of the literature only those cases are included in which enlargement of two or more glands was demonstrated. Four cases, which were included by Castleman and Mallory in their review (Cases 22, 92, 126 and 127), have been omitted because it was believed that the histologic descriptions given were not adequate. Since Castleman and Mallory's review appeared in 1935, two additional cases have been recorded at the Massachusetts General Hospital and eight others, including four from the Mayo Clinic, are included in this report. This brings the series to a total of twenty-six cases. Data on the twenty-two cases reported in the literature are given in Table 1.

* From The Mayo Foundation and The Mayo Clinic, Rochester, Minn.

The earliest reference to wasserhelle hyperplasia is that of Möller[3] in 1911. Möller mentioned the case of a woman, forty-six years of age, who died of miliary tuberculosis. Necropsy revealed two enlarged parathyroid glands measuring 4.5 by 0.5 by 0.5 cm. each. Histologically, they consisted of large cells with light cytoplasm. The clinical history was brief and included none of the manifestations of hyperparathyroidism. Gjestland,[4] in 1912, recorded one case of a man, seventy-five years of age, who died of paralysis agitans and bronchopneumonia. Asymmetrical enlargement of four parathyroid glands was present at necropsy. The glands were composed of compact, medium-sized epithelial cells with light vacuolar cytoplasm. Harbitz[5] in 1915 and Bergstrand[6] in 1921, each reported a case in which enlargement of all four parathyroid glands was observed. No significant clinical symptoms were mentioned in either

TABLE I

PRIMARY HYPERPLASIA AND HYPERTROPHY OF THE PARATHYROID GLANDS

Case	Author	Age	Sex	Surgical or Necropsy	Weight of Parathyroids	Number of Glands	Manifestations
I	Möller	46	F	N	Not recorded	2	None
II	Gjestland	75	M	N	Not recorded	4	None
III	Harbitz	75	M	N	Not recorded	4	None
IV	Bergstrand	57	F	N	400 mg., 80 mg., 145 mg. and 40 Gm.?*	4	None
V	Hoffheinz	42	F	N	Not recorded	5	Nephrolithiasis; osteitis fibrosa cystica
VI	Paul	56	M	N	70 Gm.	2	Gastrointestinal; nephrocalcinosis; histologic bone change
VII	Bergstrand	55	F	N	Not recorded	4	Nephrolithiasis; weakness and poly-dipsia; histologic bone change
VIII	Beyerinck	35	F	S and N	Not recorded	4	Osteitis fibrosa cystica
IX	Hellström	44	F	S	Not recorded	2	Osteitis fibrosa cystica; nephrocalcinosis
X	Hanke	49	F	N	Not recorded	4	Osteitis fibrosa cystica; nephrolithiasis; nephrocalcinosis
XI	Mass. Gen.	62	F	S	10.6 Gm. (subtotal)	3	Nephrolithiasis
XII	Mass. Gen.	26	M	S	19.3 Gm. (subtotal)	4	Nephrolithiasis
XIII	Mass. Gen.	55	F	S	3.4 Gm. (subtotal)	4	Nephrolithiasis
XIV	Capps	50	M	N	35.6 Gm.	3	None; mediastinal hemorrhage
XV	Mass. Gen.	41	M	S	2.47 Gm. (subtotal)	4	Nephrolithiasis
XVI	Mass. Gen.	39	M	S	6.80 Gm. (subtotal)	4	Nephrolithiasis
XVII	Mass. Gen.	57	F	S	11.20 Gm. (subtotal)	4	Nephrolithiasis; osteitis fibrosa cystica
XVIII	Mass. Gen.	63	M	S	3.39 Gm. (subtotal)	4	Nephrolithiasis; osteitis fibrosa cystica
XIX	Hellström	60	F	S	Not recorded	2	Nephrolithiasis
XX	Hellström	59	F	S	Not recorded	2	Nephrolithiasis; nephrocalcinosis; osteitis fibrosa cystica
XXI	Thyssen	51	M	S and N	Not recorded	4	Gastrointestinal; nephrolithiasis
XXII	Flink	57	F	S	23 Gm. (subtotal)	4	Osteitis fibrosa cystica; nephrolithiasis; polyuria

* The weights recorded on Bergstrand's first case are confusing. They are recorded as 400 mg., 80 mg., 145 mg. and 40 Gm. Since Bergstrand did not comment on marked variation of size, it is presumed that the fourth weight should be 40 mg. Castleman, in writing of this case, records weights as 400 mg., 80 mg., 150 mg. and 1,040 mg.

report. Histologically, Harbitz' patient revealed medium-sized epithelial cells with a vacuolated cytoplasm and in Bergstrand's patient the glands were composed of wasserhelle Zellen. In both patients oxyphil cells were absent. In these four patients no clinical or necropsy data were given that suggested hyperparathyroidism.

The first case of primary hypertrophy of the parathyroid glands to be associated with obvious clinical evidence of hyperparathyroidism was reported by Hoffheinz[7] in 1925. The patient was a woman, forty-two years of age. Manifestations of bone disease had been noted for a year and for four months she had been unable to walk. Bone cysts were present roentgenologically. There were two stones in the right kidney. Death occurred from uremia. Five parathyroid glands were found and all were enlarged. Histologically, most of the cells were wasserhelle cells but a few oxyphil cells were found. Osteitis fibrosa with "brown tumors" of the bones was present.

Paul[8] in 1931, reported the case of a man, fifty-six years of age, who had loss of appetite, weakness, fatigue and loss of approximately 28 pounds (12.7 Kg). Polydipsia was also noted. In the bones there was evidence of osteitis fibrosa. Nephrocalcinosis was observed in the kidneys. At necropsy two parathyroid glands were markedly enlarged, each weighing 35 Gm. The remaining parathyroid glands could not be identified. The histologic appearance was consistent with primary hyperplasia as the cytoplasm of the cells stained only slightly. Palisading was present.

Bergstrand[9] again in 1931, described a case in which there was enlargement of four parathyroid glands. The patient, a woman fifty-five years of age, presented the typical symptoms of hyperparathyroidism with weakness, loss of strength, obstipation, polydipsia and polyuria. Bone pain was entirely missing. The right inferior parathyroid gland was greatly enlarged and measured 4.5 by 2.5 by 3.0 cm. The left superior parathyroid gland likewise was enlarged and measured 4.5 by 2.5 by 0.5 cm. The remaining two parathyroid glands were enlarged, each weighing more than 100 mg. Histologically, indistinct cytoplasm with follicles was present. No Welsh (oxyphil) cells were present. In the bone there were changes of osteitis fibrosa. Bergstrand stated that histologically this patient did not present the picture of adenoma, as there was diffuse change in all of the parenchyma. He believed it was analogous to those changes seen in Basedow's struma.

In 1932, Beyerinck[10] reported a case which Castleman and Mallory[2] subsequently classified as an adenoma of clear cells. More recent review of the microscopic sections by Snapper[11] showed it to be typical primary hyperplasia. The patient was a woman aged thirty-five, who complained of protracted vomiting and loss of weight. No skeletal disease was found but the concentration of calcium was 21.0 mg. per 100 cc. of serum and that of phosphorus 2.0 mg. per 100 cc. of serum. A parathyroid gland the size of a coffee bean was removed at operation. Death occurred the following day and necropsy disclosed three more abnormal parathyroids varying in size from that of a coffee bean to that of a hen's egg. Nephrolithiasis was found but the skeleton was normal on microscopic examination. Snapper stated that the sections of the parathyroid glands disclosed only large water-clear cells.

Hellström[12] in 1931, reported on a patient in whom two enlarged parathyroid glands were removed at two operations. The patient was a woman of forty-four years of age who had osteitis fibrosa cystica. The histologic appearance of the two glands was consistent with that of primary hyperplasia of the parathyroid glands. This patient came to necropsy in 1942 and the findings were re-

ported in 1944 by Hellström and Wahlgren.[13] Two parathyroid glands of the size of a walnut were found at necropsy. Histologically, the predominant cell was the large, water-clear cell but small nodules were composed of chief cells and a few groups of oxyphil cells were observed. Cysts were identified. Hellström and Wahlgren called attention to the fact that two enlarged glands were removed at the time of operation in 1930 and the remaining two glands were of normal size. Twelve years later at necropsy, however, these remaining parathyroid glands were greatly enlarged and nodular. Nephrocalcinosis was also observed. This case is of particular interest because it is to date the only instance of primary hyperplasia with hyperparathyroidism in which there has been an opportunity for comparison of surgical and necropsy findings after an interval of twelve years.

Two additional cases in which primary hyperplasia was treated surgically were also reported in 1944 by Hellström and Wahlgren[13] (Cases v and viii). In each patient two enlarged glands composed of water-clear cells were removed. In the first patient there was nephrolithiasis but no bone manifestations and in the second, there was osteitis fibrosa, nephrocalcinosis and nephrolithiasis. In the first instance, the serum calcium before operation was 15.4 mg. per 100 cc. and after operation it still remained high (13.5 mg. per 100 cc.).

Hanke,[14] in 1932, presented the necropsy findings on a woman, forty-nine years of age, who had extremely far-advanced skeletal changes due to osteitis fibrosa cystica. The serum calcium was 23.4 mg. per 100 cc. The bone manifestations were classic. All four parathyroid glands were enlarged and histologically all cells were wasserhelle Zellen. There was nephrolithiasis and nephrocalcinosis.

Those cases described by Hoffheinz,[7] Paul,[8] Bergstrand,[9] Beyerinck,[10] Hellström[12] and Hanke[14] best fit the criteria of primary hypertrophy and hyperplasia of the parathyroid glands as outlined subsequently by Albright and associates.[1] It is interesting that in the reports of the earlier writers, marked emphasis was placed on the bone manifestations and lengthy descriptions of the gross and histologic appearances of the bone were given, while in many instances meager descriptions of the parathyroid glands were given.

In 1934, Albright, Bloomberg, Castleman and Churchill[1] presented data on three cases which emphasized the clinical importance of primary hypertrophy, hyperplasia and primary hyperparathyroidism* with enlargement of all parathyroid glands. They showed that surgical removal of one gland will not cure the patient of hyperparathyroidism if all four parathyroids are involved. The surgical management of these patients has been presented separately by Churchill.[15]

Capps,[16] in 1934, reported an interesting case of mediastinal, cervical and thoracic subcutaneous hemorrhage associated with multiple parathyroid tumors. The patient was a man of fifty years of age. At necropsy the hemorrhage was found to have originated within one of the parathyroid glands. Two parathyroid glands were found grossly enlarged and a third gland was found histologically. The total weight was 35.6 Gm. Their histologic structure was identical with that reported by Albright.[1] Capps stated that neither on clinical nor on necropsy finding could the existence of hyperparathyroidism be proved or disproved.

In 1935, Castleman and Mallory[2] presented a classic review of the pathologic condition of the parathyroid gland in hyperparathyroidism. They reviewed the three cases from the Massachusetts General Hos-

* Hyperparathyroidism is defined as "primary" when more parathyroid hormone is produced than the body requires and as "secondary" when an increased production of parathyroid hormone is a compensatory response to some other condition.

pital originally presented by Albright, Bloomberg, Castleman and Churchill[1] and included two more of their own from the same hospital. A comprehensive review of the literature was given. They emphasized enlargement of all four glands in certain patients who demonstrated one type of cell, the wasserhelle cell. They noted that these cells had a tendency to acinar arrangement with basal orientation of the nuclei and varied from 10 to 40 microns in diameter. The nuclei of these cells, while often multiple, were approximately of the same size. The location of the nucleus at the base of the cell produced a characteristic pattern that resembled bunches of berries. The cytoplasm was clear, except for light pink staining granular material.

Castleman and Mallory[17] in 1937, distinguished between the changes seen in the parathyroid glands secondary to long-standing renal insufficiency and those associated with primary hyperplasia. In the glands enlarged secondarily as a result of renal insufficiency, the gland histologically is composed of chief cells. Vacuolization of the cytoplasm may occur but the cell does not reach the size of those in patients with primary hyperplasia in whom the large water-clear cell is a constant feature.

The surgical aspects of primary hypertrophy and hyperplasia of the parathyroid glands were reviewed by Cope[18] in 1935, and again by Churchill and Cope[19] in 1936. Albright, Sulkowitch and Bloomberg[20] in 1938, presented the clinical aspects of five cases previously reported from the Massachusetts General Hospital and of a sixth case from the same hospital. The number of male and female patients was equal and the age ranged from twenty-six to sixty-two years. Renal stones were present in all six patients and bone changes were present in only one. In all patients the treatment was surgical. In one patient three enlarged glands were identified, while in the other patients four enlarged glands were found. The amount of parathyroid tissue removed at operation ranged from 2.47 to 19.3 Gm. The remaining parathyroid tissue ranged from an estimated 0.12 to 0.5 Gm. In all patients the typical histologic picture with large water-clear cells was present. It was Albright's[20] opinion at this time that enlargement of the glands was the result of hypertrophy rather than of hyperplasia.

The surgical treatment of hyperparathyroidism was discussed again by Cope[21] in 1941. He emphasized that enlargement of four glands may occur in primary hyperplasia. In 1943, Cope,[22] reported the seventh case of primary hypertrophy and hyperplasia of the parathyroid glands from the Massachusetts General Hospital. Among seventy patients with hyperparathyroidism primary hypertrophy was found seven times. In the seventh instance the patient was a man, sixty-three years of age, who had renal stones and manifestations of osseous disease. All four glands were enlarged and 3.39 Gm. of parathyroid tissue was removed. The histologic appearance was identical with that previously described.[2]

Thyssen[23] described a case which he called adenomatous hyperplasia of all parathyroids. From his description it is another instance of typical generalized hyperplasia of clear cells. The patient, a man aged fifty-one, had typical generalized osteitis fibrosa cystica and a serum calcium value of 14.1 mg. per 100 cc. Two parathyroid glands measuring 3 by 1 cm. were removed at operation, one from each side. Anuria developed and the patient died four days following operation. At necropsy a third parathyroid gland, measuring 1.5 by 0.75 by 0.5 cm., was found on the right and a fourth gland, measuring 3 by 2 cm., was found in the superior mediastinum. On histologic examination all of the parathyroid

glands were similar in structure and were composed entirely of large, clear polygonal cells. There was no nephrolithiasis or nephrocalcinosis.

Flink[24] in 1945, reported the case of a woman, fifty-seven years of age, who had renal stones and bone changes. At the time of the first operation one gland weighing 3.0 Gm. was removed. As the clinical and chemical evidence of hyperparathyroidism persisted a second operation was performed. Two glands weighing 18.0 and 2.0 Gm., respectively, were removed. A fourth gland which was apparently normal in size was identified. The histologic picture of all parathyroid tissue was identical with that described in detail before. While the serum calcium dropped to normal after the second operation the bone pain persisted, the phosphorus remained low and the alkaline phosphatase and urinary excretion of calcium continued high. These findings might suggest the presence of additional hyperfunctioning parathyroid tissue.

At the Mayo Clinic four cases of primary hypertrophy and hyperplasia of the parathyroid glands have been described. During the same period sixty patients with proved hyperparathyroidism have been observed. The first case of primary hypertrophy of the parathyroids was described by Rogers[25] in 1946 and the second case by Rogers, Keating, Morlock and Barker.[26] More detailed reports of the third and fourth cases are now in the press. A brief summary of the four cases follows:

CASE REPORTS

Case I (reported by Rogers[25]). The patient was a man aged fifty-three. He was admitted June 4, 1945. Gastrointestinal symptoms, manifested by vomiting and epigastric pain, had been present for two years. Roentgenologic examination visualized a duodenal ulcer. Vomiting increased with institution of Sippy diet and ulcer regimen. Gastric resection was performed because of the duodenal ulcer. Vomiting reappeared three days after the operation. This persisted and uremia developed before death. Death occurred July 10, 1945.

At necropsy, parathyroid hyperplasia was observed. There was asymmetrical enlargement; besides the four normal parathyroid glands there were five accessory glands. The largest gland weighed 14.9 Gm. and their total weight was 20.32 Gm. Histologically, all of the cells were large, clear cells arranged in masses, cords and at times in an alveolar pattern. There was metastatic calcification of the dura mater and nephrocalcinosis. No osseous changes could be demonstrated. Because hyperparathyroidism had not been suspected during life, no data were observed on values of calcium and phosphorus in serum or urine. The necropsy findings, however, were regarded as strongly suggestive of hyperparathyroidism.

Case II (reported by Rogers, Keating, Morlock and Barker[26]). The patient was a man sixty-eight years old whose final admission was on October 1, 1945; he had gangrene of the left great toe. In 1919, gastro-enterostomy had been performed for a duodenal ulcer. In 1943, pain in the right foot, hip, ankles, knees and shoulders developed. In May, 1945, there was recurrence of epigastric pain, nausea and vomiting. Polydipsia and polyuria developed four months prior to last admission. Urea was elevated at the time of admission and rose from 182 to 258 mg. per 100 cc. of blood. Death occurred October 5, 1945.

At necropsy there was parathyroid hypertrophy. Six parathyroid glands were identified. The enlargement was fairly symmetrical, the two largest glands weighing 30.9 Gm. and 14.2 Gm., respectively. The total weight of the parathyroid glands was 47.56 Gm. Histologically, all of the glands were composed of large, water-clear cells. Nephrocalcinosis and multiple pancreatic calculi were present. There was osteitis fibrosa. A peculiar calcification of the intimal elastic lamina was present in many of the arteries. In this instance, as in the preceding, hyperparathyroidism was not suspected before the patient's death and clinical confirmation of its existence was not obtained. Hyperparathyroidism can be assumed with reasonable certainty from the necropsy findings.

CASE III (Case LV, reported by Black and Sprague[27]). The patient was a woman, forty-eight years of age, who registered at the clinic May 7, 1946, complaining of pain in the right hip and both legs of two years' duration. Examination disclosed multiple renal calculi in the right kidney and generalized osteitis fibrosa cystica. The concentration of calcium in the serum was 12.4 mg. per 100 cc.; inorganic phosphorus, 0.9 mg. per 100 cc. and alkaline phosphatase, 5.7 Bodansky units. Serum proteins were 6.9 Gm. per 100 cc. and the Sulkowitch test suggested pronounced hypercalciuria.

Operation was performed May 25th by Dr. Black. On the right side a large mass weighing 50 Gm. was found. It was located behind the right lobe of the thyroid and extended from the level of the superior pole well into the superior mediastinum. It was lobulated and had many small projections on its surface. Its form gave the impression of an upper and a lower portion; since no other mass was found on the right it was assumed that this may have represented both the upper and the lower gland. On the left side two masses of similar tissue were found; an upper mass estimated to weigh about 300 mg. and a lower mass weighing 4 Gm. All, except the left upper mass, were removed and were found on examination to consist entirely of typical water-clear cells of primary hyperplasia.

The postoperative course was essentially uneventful except for mild paresthesias on the third day. The serum calcium twenty-four hours after operation was 9.3 mg. per 100 cc. and two months later it was still normal.

CASE IV (Case XIX, to be reported by Pemberton and Keating[28]). The patient was first seen in 1940, at the age of thirty-one. He had had recurrent renal stones since 1936 and a recurrent duodenal ulcer since 1937. At the time of his first admission in 1940, right pyelolithotomy was performed for the removal of numerous calcium oxalate stones. The serum calcium at this time was 10.8 mg. per 100 cc. but a diagnosis of hyperparathyroidism was not suspected. He returned in 1943, because of recurring left renal colic. The serum calcium at this time was 11.5 mg. per 100 cc.; serum phosphorus, 2.4 mg. per 100 cc.; alkaline phosphatase, 2.8 mg. Bodansky units and serum proteins, 7.1 Gm. per 100 cc. The average daily excretion of calcium with the patient on a weighed diet was 211 mg. There was no evidence of skeletal disease.

An operation was performed July 8, 1943, by Dr. Pemberton. A soft parathyroid tumor was found behind the upper pole of the right lobe of the thyroid. It measured 2.5 by 1.0 by 0.75 cm. Because of its unusually soft consistency, Dr. Pemberton suggested the possibility that it might be hyperplastic. However, exploration did not disclose any other parathyroid tissue and the pathologic report made at the time was parathyroid adenoma.

The patient had an uneventful postoperative course. However, the abnormalities observed in the chemical composition of the blood and urine persisted unchanged and the presence of more hyperfunctioning parathyroid tissue was suspected. A low calcium, low phosphorus diet was prescribed and the patient was advised to return for periodic observation, which he did. For the next two years he remained well, despite the persistence of mild hypercalcemia. The average serum calcium was 10.5 mg. per 100 cc. and hypercalciuria was present (average daily excretion 182 mg.). The urinary tract remained normal. In the absence of further symptoms, neither the patient nor his physicians were anxious to resume the search for another parathyroid tumor, particularly when it was believed that mediastinal exploration would be required.

In February, 1946, the patient again began to have right renal colic. He returned for further examination in June and was found to have a stone 1 cm. in diameter in the pelvis of the right kidney with extensive destruction of the renal parenchyma. The serum calcium was 10.5 mg. per 100 cc.; serum phosphorus, 2.7 mg. per 100 cc. and the excretion of calcium 254 mg. per day. No evidence of bone disease was found.

A clinical diagnosis of persistent hyperparathyroidism was made and further operation was advised because of the extensive renal damage which the previous policy of temporizing had permitted. It was assumed that another parathyroid tumor would be found but because of our recent experience with Case III, the sections of the first tumor were reviewed before operation

and found to be typical of primary hyperplasia. At operation (July 3, 1946) an enlarged, left upper parathyroid was found, another enlarged gland was found at the left lower pole and a small gland was found in the right inferior position. The left superior mass was resected, leaving a tiny tag of tissue behind. The resected portion weighed 250 mg. The left inferior mass was entirely removed and found to weigh 200 mg. The small right inferior mass was also removed. Histologically, the vast majority of cells in all parathyroid tissue removed were large, clear cells but a few small nests of chief cells were identified in two of the glands.*

Postoperatively, the patient had moderate discomfort from paresthesias and exhibited positive Chvostek and Trousseau signs. No treatment was required for tetany. The serum calcium fell to 8.0 mg. per 100 cc. and the serum phosphorus rose to 4.5 mg. per 100 cc. Hypercalciuria persisted, however, the last determination before dismissal being 150 mg. per day.

ANATOMIC CONSIDERATIONS

The gross appearance of the parathyroid glands in those patients with primary hyperplasia is frequently characterized by the presence of cysts and pseudopods. This was demonstrated in those cases reported from the Massachusetts General Hospital and was likewise present in three of the four patients seen at the Mayo Clinic. The total weight of the parathyroid tissue may vary greatly, from 2 or 3 Gm. in one patient to others in which the weight exceeded 50 Gm. The greatest recorded weight of 70 Gm. occurred in Paul's[8] case. While enlargement of all parathyroid glands is characteristic of primary hyperplasia this enlargement may be minimal in several of the glands and extreme in the remainder. In our second patient fairly symmetrical enlargement of the parathyroid glands on each side was observed; in our third, asymmetrical enlargement was present with the largest mass (which was believed to be a fusion of the right superior and the right inferior parathyroid gland) weighing 50 Gm. In this case the left inferior parathyroid gland weighed 4 Gm. and the left superior parathyroid gland was estimated to weigh 300 mg. Smaller degrees of enlargement, however, are of clinical importance, for in our fourth patient removal of two glands weighing 250 mg. and 200 mg., respectively, was sufficient to relieve persistent chemical and clinical evidences of hyperparathyroidism.

In the cases reported elsewhere, as in our own, primary hyperplasia of the parathyroid glands exhibits a basic histologic pattern. Nevertheless, our four patients show some minor variations from the basic pattern. These variations in appearance may be demonstrable in different glands from the same patient.

The most constant feature is the presence of very large clear cells,* the diameters of which range from 10 to 40 microns, which formed the major part of all glands in our patients. However, these cells may vary markedly in size so that in some regions they do not appear much larger than the water-clear cells found in small numbers in normal parathyroid tissues. In most regions the cytoplasm is water-clear but in some cells small eosinophilic granules and fine strands are present. The nucleus is for the most part constant in size and averages about 6 to 7 microns; however, some nuclei are larger

* Hellström and Wahlgren[13] noted similar nests of chief cells in what otherwise appears to have been typical primary parathyroid hyperplasia. In Hellström and Wahlgren's patient this observation was made at necropsy twelve years after surgical resection of two glands; in both their patient and ours, nests of chief cells followed surgical resection.

* The terms wasserhelle and large water-clear cells have both been used interchangeably in this report to describe the histologic appearance of the cells in primary hyperplasia. Most of the older papers, especially those written in German, refer to wasserhelle Zellen. Inasmuch as they are probably derived from chief cells and do not represent embryologically distinct cells, there does not appear to be any value in the retention of the term wasserhelle. It seems preferable, therefore, to speak of these cells as large clear cells.

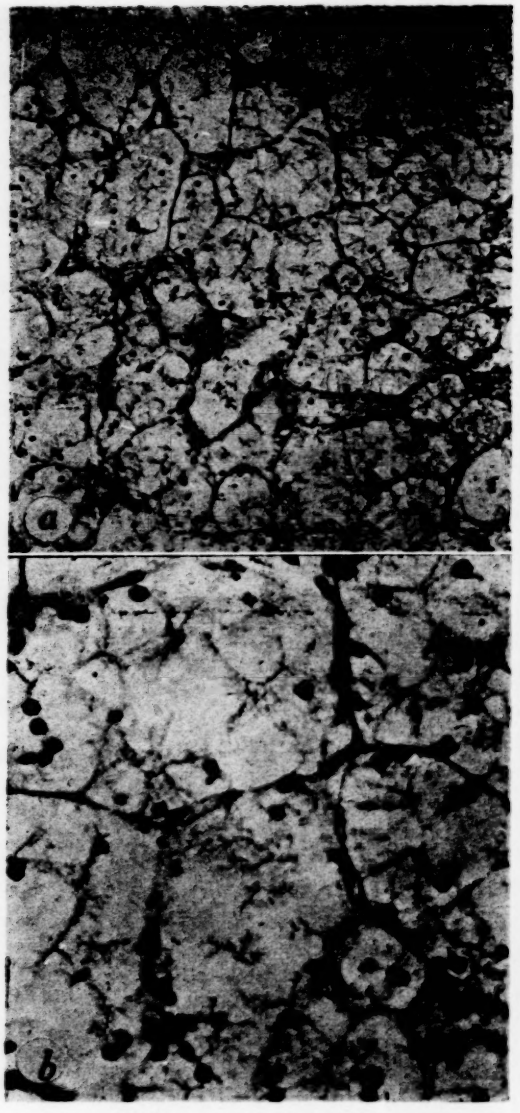


FIG. 1*a*, Primary parathyroid hyperplasia (Case III); alveolar pattern (× 115); *b*, higher magnification with typical large, water-clear cells (× 350).

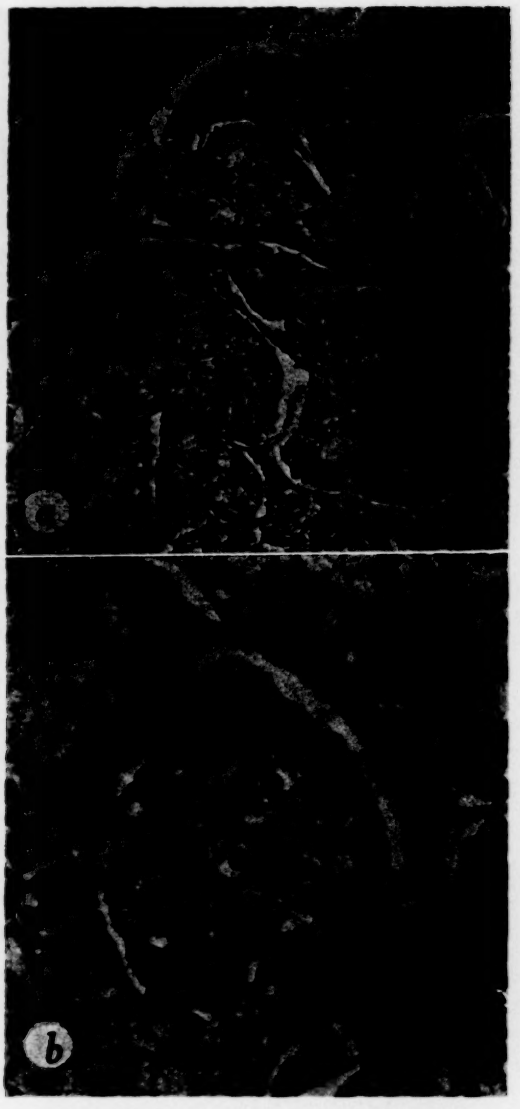


FIG. 2*a*, Primary parathyroid hyperplasia (Case II). Pseudoglandular pattern (× 115); *b*, higher magnification with basally oriented nuclei (× 350).

(8 to 9 microns), but none reach the size of the giant nuclei sometimes seen in adenomas. The basal orientation of the nuclei is one of the most constant features.

There is some variation in the grouping of the cells. Four distinct patterns may be found, with one gland frequently showing more than one of them. The first and most characteristic pattern is an alveolar arrangement. The water-clear cells form a lacelike pattern in which one is able to see only the nucleus and the fine eosinophilic cell membrane. (Fig. 1 *a* and *b*.) There may be rupture of the basement membrane, producing a picture somewhat like that of pulmonary emphysema. This was first described by Castleman and Mallory.[2] The second pattern is characterized by grouping of cells into a pseudoglandular formation. Here, the basally oriented nuclei give a characteristic appearance. (Fig. 2 *a* and *b*.) The third pattern is a more compact arrangement of

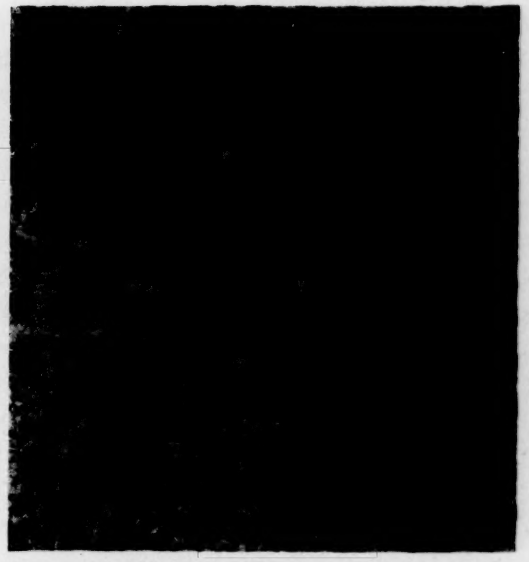


FIG. 3. Primary parathyroid hyperplasia (Case I); compact pattern (× 350).

the cells which is a relatively uncommon grouping. The cells here are smaller and there is more eosinophilic material within the cytoplasm, although the water-clear nature of the cells is readily identified. (Fig. 3.) The fourth pattern shows varying sized cysts and hemorrhage within these. (Fig. 4 *a* and *b*.) The connective tissue in most regions is sparse, appearing as delicate strands of reticulum lying between the epithelial cells and nearby capillaries. In other regions the connective tissue increases in density greatly, separating epithelial cells and capillaries. Chief cells were absent in all our patients except the fourth one (Fig. 5 *a* and *b*), where a few nests were identified.

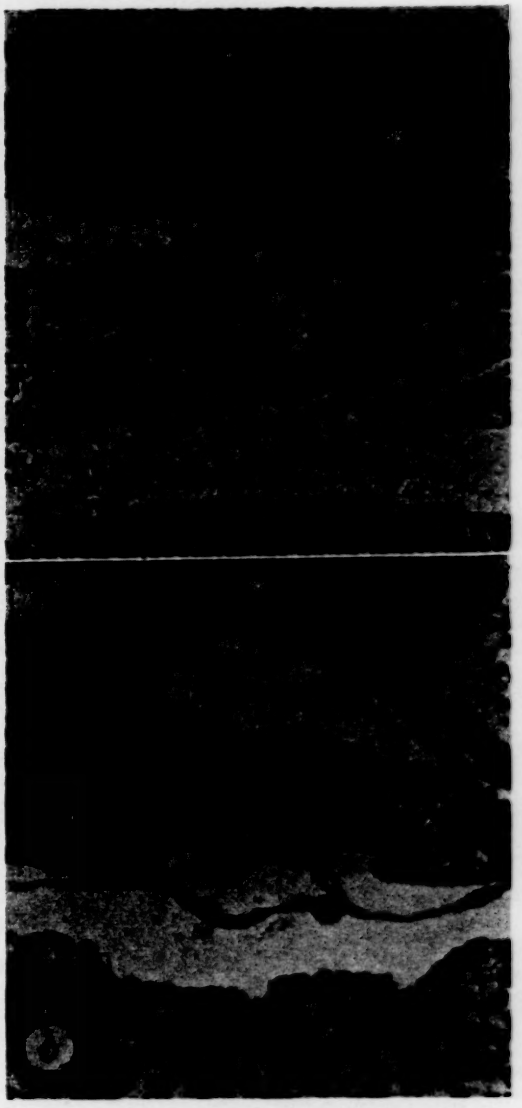


FIG. 4*a*, Primary parathyroid hyperplasia (Case II); cystic pattern; two portions of cysts in upper and lower portion, filled with erythrocytes (× 115); *b*, higher magnification of upper portion reveals edge of cyst lined by cells with basally oriented nuclei. The cyst is filled with erythrocytes (× 350).

HYPERTROPHY VERSUS HYPERPLASIA

Albright and his associates have suggested that the pathologic condition of the parathyroids under discussion is largely,[20] or entirely[29] due to hypertrophy. The chief cell of the normal parathyroid gland, according to Castleman and Mallory,[17] has a mean diameter of 7 microns. Albright and his associates[20,29] have stated that the cells in primary hyperplasia have a diameter four to five times the normal diameter. Since, as they pointed out, the volume of a sphere increases as the cube of the radius, one could expect simple hypertrophy alone to account for an increase in the volume of parathyroid tissue up to sixty-four or one hundred twenty-five fold. Since the weights of the parathyroid glands in their patients varied from thirty to one hundred forty times normal, they believed that hyper-

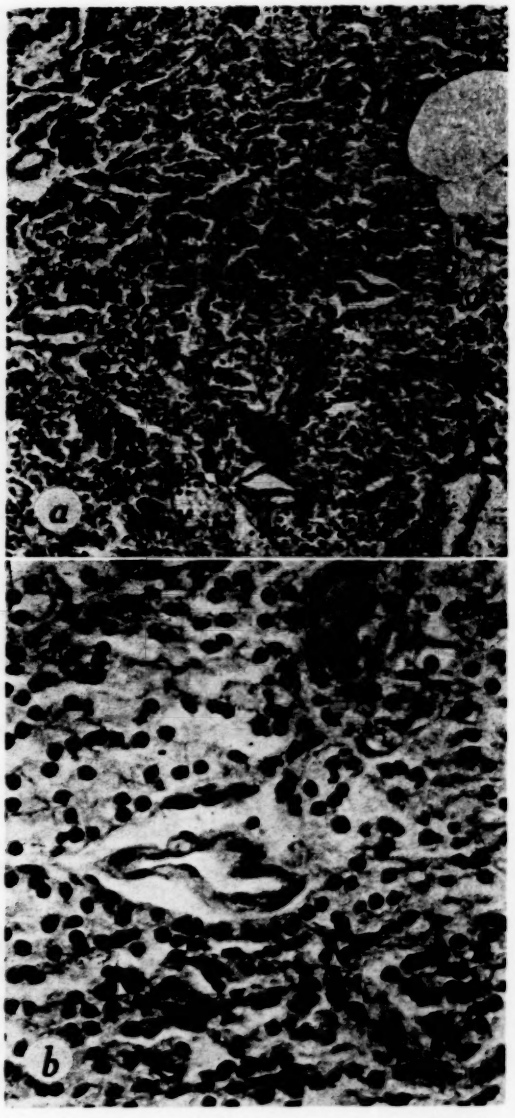


FIG. 5*a*, Nests of chief cells in parathyroid glands from Case IV (× 115); *b*, higher magnification (× 350).

trophy alone and not hyperplasia accounted for the enlargement.

The parathyroid tissue from the two necropsy cases which we have presented weighed 20.32 and 47.56 Gm. respectively, while that from the two surgical cases weighed 54 and approximately 3 Gm., respectively, disregarding the tissue left at operation. The mean weight of normal parathyroids is given as 117.6 mg. for men and 131.3 mg. for women.[30] On the basis of these figures the glands in our patients are, in order, 170, 400, 410 and 26 times normal. After allowing for the cysts which they contain, the two largest are still too large to explain by simple hypertrophy, even if one accepts Albright's figure for a mean cell size of 40 microns. Moreover, direct measurement of mean cell size in these patients showed the mean diameter to be 21 microns, even though individual cells varied in size from 10 to 35 microns. The maximal increase in volume of parathyroid tissue which could be explained as hypertrophy alone was, therefore, twenty-seven times, which could have accounted for the weight observed in only the last patient. Further evidence in favor of hyperplasia is the fact that the total weights of the parathyroid tissue in our patients varied from 3 to 54 Gm., despite which the mean cell diameter was 20 to 21 microns in all instances. If hypertrophy alone, and not hyperplasia, was the cause of the parathyroid enlargement, one would expect a much greater mean cell diameter in those patients in whom there was the greatest mass of parathyroid tissue; this was not the case. The gross appearance of the glands was in itself suggestive of hyperplasia, particularly in the case of the larger ones. Irregularities of form and shape and the numerous projections and pseudopods were more consistent with overgrowth of cells than with simple enlargement of preexisting cells. We, therefore, believe the condition to be one of hypertrophy *and* hyperplasia, with the latter playing the predominant rôle.

Pathologically at least, primary hyperplasia of the parathyroid glands appears to be analogous to the parenchymatous hypertrophy and hyperplasia of the thyroid which accompanies exophthalmic goiter and the adrenal cortical hyperplasia sometimes encountered in Cushing's disease. Whether (as in exophthalmic goiter) surgical resection will be followed by further hyperplasia and recurrence in any substan-

tial proportion of patients will be an important question for future studies to settle. Albright's experience with six patients did not disclose any tendency toward recurrence. He was impressed with the fact that the disease, once established, appeared to persist without appreciable variation and that conservative resection effected partial improvement which, while inadequate, was sustained. In Hellström's[12] first patient, however, there was almost certainly recurrence of parathyroid enlargement. At two operations in 1930 and 1931, two large, walnut-sized parathyroids were removed. A third, the size of a bean, was noted. At necropsy in 1942, two more very large glands were found which Hellström and Wahlgren[13] stated must have enlarged in the interim. The data suggest, however, that the hyperparathyroidism persisted rather than recurred, since the postoperative values for calcium in serum remained somewhat elevated.

Our short experience with two surgical cases has thrown no further light on this matter. It is noteworthy that in our Case IV, a second operation disclosed three masses of parathyroid tissue which had not been observed at the initial exploration three years before. It might be argued that these masses had appeared as a consequence of hyperplasia after resection of the original relatively larger mass. The clinical course of the patient, however, did not favor this interpretation. Instead of the remission and recurrence which should have taken place if the foregoing explanation were valid, the patient had an unabated persistence of the original chemical abnormalities. The remarkable feature, in fact, is that no significant reduction of serum calcium or urinary calcium followed the resection of approximately 3 Gm. of parathyroid tissue, whereas the subsequent removal of an additional 450 mg. was followed by precipitate fall of serum calcium and symptoms of mild tetany. The persistence of mild hypercalciuria, despite a normal serum calcium, is a disturbing feature which cannot thus far be explained.

On the assumption that the condition was hypertrophy alone, Albright's chief concern in the surgical management of these patients has not been recurrence, but the fear that subtotal resection sufficient to control the disease might be followed by subsequent disappearance of hypertrophy in the remnant, which would leave the patient with an inadequate quantity of parathyroid tissue and perhaps with permanent parathyroid insufficiency. There has not, to the best of our knowledge, been any evidence that this has occurred.

MORPHOLOGIC DIAGNOSIS

The gross and microscopic appearance of primary parathyroid hyperplasia must be differentiated from several entirely different pathologic entities which it somewhat resembles. These include hyperplasia of the chief cells of the parathyroid glands, metastasis of a renal cell carcinoma to the thyroid gland and adenoma of the parathyroid glands composed of large clear (wasserhelle) cells.

There may be enlargement of all four parathyroid glands in long-standing renal insufficiency. This type of secondary hyperplasia has been described by Castleman and Mallory.[17] Histologically, the parathyroid glands in patients with secondary hyperplasia due to renal insufficiency are composed of chief cells alone, or in combination with oxyphil cells, in contrast to the large water-clear cells seen in those patients with primary hypertrophy. The typical appearance of chief cell hyperplasia due to long-standing renal insufficiency is shown in Figure 6 *a* and *b*. This gland was removed at necropsy from a patient sixteen years of age. Renal infection had occurred at two years of age and the terminal concentration

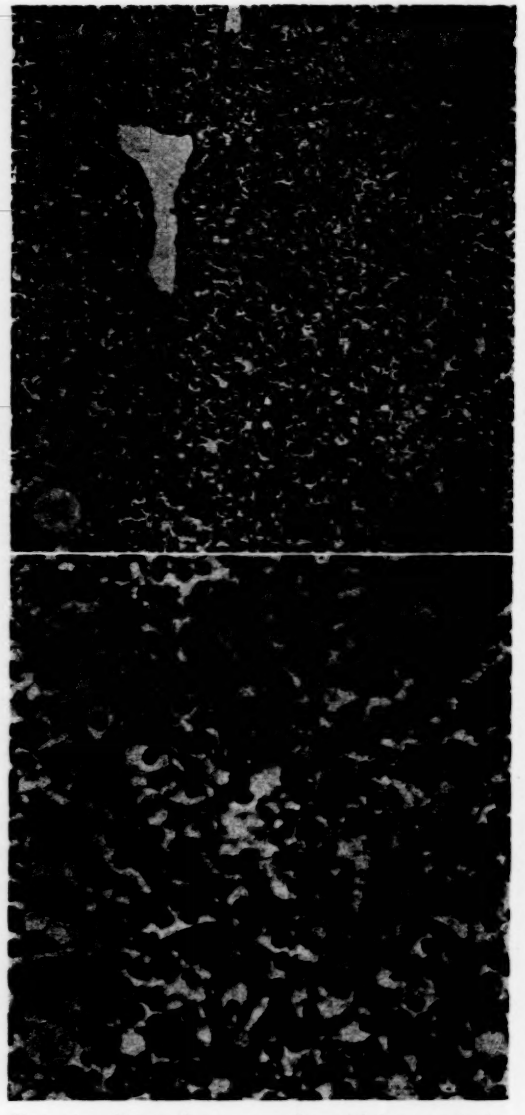


FIG. 6*a*, Secondary parathyroid hyperplasia due to renal insufficiency; chief cells, at times vacuolated (× 120); *b*, higher magnification of chief cells, a few revealing vacuolated cytoplasm (× 350). The small diameter of the cells is in marked contrast to the very large cells of primary hyperplasia. Compare with Figures 1*b*, 2*b*, 3 and 4*b* which are of the same magnification.

of urea was 600 mg. per 100 cc. of blood. The findings of healed pyelonephritis and hyperplasia of parathyroid glands were present.

Hyperplasia of chief cells indistinguishable from that accompanying renal disease is also encountered in calcium deficiency states, including rickets (avitaminosis D), osteomalacia, sprue, pregnancy and lactation.

Renal cell carcinoma with metastasis to the thyroid may cause confusion if only histologic sections of the thyroid are examined. Castleman and Mallory[2] have also emphasized this and pointed out that the histologic appearance of primary hyperplasia of the parathyroid glands may resemble and actually be misdiagnosed as metastatic renal cell carcinoma. Metastasis of a renal cell carcinoma to the thyroid is not common. Long and Black[31] in 1945, were able to find only eleven recorded instances of its occurrence. One of the most helpful differentiating features histologically is the basally oriented smaller, darker nucleus of the cells in instances of primary hyperplasia.

In the histologic diagnosis it is also to be considered that a parathyroid adenoma may consist almost entirely of large clear cells. Differentiation between an adenoma composed of large clear cells and primary hyperplasia of large clear cells depends on the demonstration of the enlargement of all parathyroid tissue in the case of the latter. The clinical course of Case IV illustrates the importance of this differentiation. Castleman and Mallory[2] have reported one case of their own of an adenoma consisting solely of wasserhelle cells and cited eleven possible examples occurring in the literature. It is probable that the case originally reported by Wilder, Camp, Robertson and Adams[23] is an example of this. The patient was a woman forty-eight years of age. Bone manifestations were marked and the alkaline phosphatase varied from 4 to 61.7 Bodansky units. At operation a tumor weighing 5 Gm. was removed. Histologically, it was composed almost entirely of cells with clear cytoplasm sometimes arranged in acinar formation. There was postoperative tetany followed later by severe gastrointestinal manifestations, including nausea, vomiting, cramps and diarrhea. These symptoms were

aggravated by administration of calcium and intravenous administration of sodium phosphate. Death occurred seventy-seven days after operation. At necropsy three enlarged parathyroid glands the size of a split pea were identified and histologically reported as being identical with the tumor which had been removed surgically. The bone changes were histologically consistent with osteitis fibrosa. Castleman and Mallory[2] reviewed this case (Case 127) in their series without having the opportunity of examining the slides and considered it an example of generalized hyperplasia of the clear-cell type. We have reviewed the histologic slides in this case. The gland removed at operation consisted entirely of large clear cells; however, in the glands removed at necropsy chief cells predominated and large clear cells were in a minority. We believe that this was an adenoma of one parathyroid gland of the wasserhelle cell type with secondary hyperplasia of the three remaining glands.* The coexistence of hyperfunctioning adenoma of one parathyroid gland with secondary hyperplasia of the remainder in the absence of renal insufficiency is most unusual. Usually the nonadenomatous glands grossly are either normal or atrophic in appearance. It is possible, therefore, that hyperplasia took place in the remaining parathyroid tissue after surgical removal of the tumor. The secondary hyperplasia in this case may have been caused by the low blood calcium maintained as a result of the extreme postoperative demands of the bones for calcium, or as a result of intravenous treatment with sodium phosphate or both. In this connection it is interesting to note that secondary parathyroid hyperplasia has been produced in rabbits by the parenteral administration of phosphate.[33]

Throughout this report the term "primary" hyperplasia has been used to distinguish the condition from secondary hyperplasia in which the histologic appearance is different. The use of the term primary seems justified at this time because the exciting cause is unknown. It is probable that an etiologic agent or agents may be found in the future and then the term primary will no longer prove applicable. Albright and his associates[1] originally felt that the pituitary gland might well be the primary stimulating factor but in a subsequent report[20] they expressed the belief that the etiologic factor is unknown. In only our first patient was the pituitary gland available for study and it was histologically normal; the adrenal glands were grossly and histologically normal in the first two patients and in none of our four subjects were there clinical manifestations of disturbed function of the pituitary. In a review of the literature, Pope and Aub[34] concluded "that the evidence for a relation between the parathyroid glands and the anterior pituitary is neither consistent nor conclusive. If such a relation exists, it is probably not an extremely close one, for the former appear to be able to function even when the anterior pituitary is removed."

In some instances of secondary parathyroid hyperplasia, there is extensive vacuolization of the cytoplasm of the chief cells, which like the hyperplastic process *per se* may represent a cellular response to the stimulus which induces hyperfunction (elevated serum phosphorus, lowered serum calcium or both?). In these instances the vacuolated cells resemble in size and nuclear characteristics the normal chief cell but their clear cytoplasm resembles that of the much larger water-clear cell of primary hyperplasia. Perhaps the remarkable cellular changes in patients with primary hyperplasia represent merely an extensive degree of the same type of response to stimulation;

* Dr. Benjamin Castleman kindly examined the slides in this case and was in entire agreement with this diagnosis.

in this case to a stimulus of unknown character and origin.

The case reported by Lober, Hertzog and Rice[35] is an example of vacuolization of chief cells in secondary parathyroid hyperplasia due to renal insufficiency. Their patient had hyperparathyroidism with osteitis fibrosa cystica. A parathyroid adenoma composed of chief cells was removed. Death from renal insufficiency occurred three years later. Nephrocalcinosis with tubular obstruction was marked. The parathyroid glands removed at necropsy were described as consisting almost entirely of wasserhelle cells, although the evidence in this case pointed to renal insufficiency as a cause for the enlargement. Measurements of cell diameters were not given and the magnification of the photomicrographs was not stated. Through the kindness of Dr. A. J. Hertzog we have had the opportunity of reviewing the slides. The mean diameter of the cells in the parathyroid glands removed at necropsy was found to be 10 to 12 microns, with the largest cells not exceeding 15 to 16 microns. Their size is considerably smaller than that of the large water-clear cell typical of primary hyperplasia. We agree with Lober, Hertzog and Rice that the glands examined at necropsy represent secondary hyperplasia due to renal insufficiency and believe the clearness of the cytoplasm represents vacuolization of chief cells as described by Castleman and Mallory. We do not believe that they should be termed wasserhelle cells or confused with primary hyperplasia as they are much smaller.

CLINICAL CONSIDERATIONS

In the majority of the reported cases of primary hyperplasia the patients have had obvious hyperparathyroidism. Bergstrand[9] was the first to suggest that primary parathyroid hyperplasia is the counterpart in the parathyroids of exophthalmic goiter in the thyroid. At the present time this concept appears to be justified. We believe that the histologic picture of primary hyperplasia always indicates a primary excess of parathyroid hormone. However, it must be pointed out that in five (Cases I, II, III, IV, and XIV in Table I) of the twenty-two cases reported elsewhere neither clinical nor pathologic evidences of hyperparathyroidism were described. The first four of these reports appeared before 1925, when hyperparathyroidism was first described as a clinical entity and the fifth patient died before careful clinical appraisal could be concluded. As all five were necropsy cases the absence of any notation regarding bone lesions or nephrolithiasis may be significant but such omissions do not exclude entirely the possibility that some degree of previous hyperparathyroidism might have been present in these instances also. In the first two cases reported from the clinic, hyperparathyroidism was not suspected or confirmed during life but the necropsy findings made a diagnosis of hyperparathyroidism highly probable.

It is important to consider whether the hyperparathyroidism resulting from primary hyperplasia differs either qualitatively or quantitatively from that resulting from neoplastic lesions of the parathyroids. Keating and Cook,[36] on reviewing twenty-four cases of primary hyperparathyroidism (twenty-three of which were due to parathyroid tumor) which were seen at the Mayo Clinic during a period of two and one-half years, found that in a third of them there was classical osteitis fibrosa cystica; in another third, there was minimal bone disease, and in a third there was no clinical evidence of bone disease whatever. In twenty-two of the twenty-four cases there was some degree of renal involvement. These observations agree closely with those of Albright and his associates but are in marked contrast to the majority of cases of hyperparathyroidism reported from other sources.

In most published cases of hyperparathyroidism there has been severe and usually extreme osteitis fibrosa cystica; despite Albright's contributions, most other observers have not recognized the disease in the absence of severe skeletal disease. We believe, as Albright does, that this is so because the disease is not intensively sought, as it should be, among patients presenting themselves because of nephrolithiasis or nephrocalcinosis.

In twenty-one of the twenty-six cases of primary hyperplasia there have been findings which warrant a diagnosis of hyperparathyroidism; in nine of these classic osteitis fibrosa cystica has been present, in three there have been milder degrees of skeletal involvement evident only on histologic examination and in nine there has been no evidence of skeletal disease. In sixteen there has been nephrolithiasis, in four there has been nephrocalcinosis and in one there has been no evidence of renal disease. So far as present experience indicates, therefore, there appears to be no reason to consider that the hyperparathyroidism of primary hyperplasia is qualitatively any different in its manifestations from that resulting from tumor. By the same token there are no clinical means by which a patient shown to have the clinical and chemical manifestations of hyperparathyroidism can be predicted to have hyperplasia instead of neoplasia; the surgeon must be prepared to encounter either lesion in every patient in whom exploration is performed for hyperparathyroidism.

Analysis of the data available does not justify a definite conclusion that, in the aggregate, hyperplasia produces a less intense form of hyperparathyroidism than tumor but there are several reasons for inferring that this may be the case. In the first place, in only two of the earlier cases of osteitis fibrosa cystica due to hyperplasia did the bone disease reach the extreme, deforming proportions described in many of the cases due to parathyroid tumor. In the second place, it is noteworthy that in the impressive series of patients with hyperparathyroidism observed at the Massachusetts General Hospital, where careful study has led to the recognition of the disease in milder forms which presumably might have been overlooked elsewhere, parathyroid hyperplasia has been encountered surgically seven times and accounts for approximately 10 per cent of the patients having hyperparathyroidism; in five of the seven patients there was no skeletal involvement. At the Mayo Clinic prior to 1943, hyperparathyroidism was diagnosed fourteen times in fourteen years; in all but one of the patients there was relatively severe bone disease and all were due to tumor. Since 1943, as a result of careful search for the disease, particularly in patients who had renal stones, hyperparathyroidism has been encountered in forty-three surgical and three necropsy cases, the skeletal manifestations of which have been, at least on the average, very much milder than those in earlier series. In two of the forty-three surgical and two of the three necropsy cases the lesion has been primary hyperplasia. Our recent experience, therefore, has been comparable with that of Albright.

By contrast, only ten of all of the cases of hyperparathyroidism reported from other sources have proved to be due to hyperplasia and only six of these, Beyerinck's,[10] the three of Hellström[12] and those of Thyssen[23] and Flink,[24] have been surgical cases. When the milder and less extreme forms of hyperparathyroidism are sought, hyperplasia would appear to account for 5 to 10 per cent of the patients but in the literature as a whole it accounts for an insignificant fraction.

In the two necropsy cases of primary hyperplasia which we have reported, the chief manifestations which were afterward attributed to hyperparathyroidism were gas-

trointestinal. The possibility that these manifestations may complicate the treatment of hyperparathyroidism or may confuse the diagnosis, as well as their importance, has been emphasized earlier.[25,26] The occurrence of gastrointestinal manifestations probably attributable to hyperparathyroidism in two of four patients who had hyperplasia might appear significant. However, of the twenty-two cases of hyperplasia observed elsewhere, in only those of Paul[8] and Beyerinck[10] is the patient mentioned as having major gastrointestinal symptoms. It is curious to note, however, that in three of our four cases of hyperplasia there were or had been active duodenal ulcers. We have noted the coexistence of duodenal ulcers in approximately one third of all the patients with hyperparathyroidism who have been seen at the clinic. This association seems too frequent to be coincidence but one can only conjecture as to its meaning.

SUMMARY

Primary hyperplasia of the parathyroid glands is a distinct pathologic entity. Twenty-two cases have been collected from the literature; the morphologic and clinical aspects of these and four additional cases seen at the Mayo Clinic have been discussed. Primary hyperplasia must be differentiated from parathyroid adenoma composed of clear cells, from metastatic renal cell carcinoma to the thyroid and from secondary parathyroid hyperplasia. The question of hypertrophy versus hyperplasia has been discussed; evidence is given for assuming that both are present but that the latter predominates. The clinical implications of primary hyperplasia are discussed. In twenty-one of twenty-six patients primary hyperplasia was accompanied by primary hyperparathyroidism; it is probable that the condition always represents primary parathyroid hyperfunction.

REFERENCES

1. Albright, Fuller, Bloomberg, Esther, Castleman, Benjamin and Churchill, E. D. Hyperparathyroidism due to diffuse hyperplasia of all parathyroid glands rather than adenoma of one; clinical studies on three such cases. *Arch. Int. Med.*, 54: 315–329, 1934.
2. Castleman, Benjamin and Mallory, T. B. The pathology of the parathyroid gland in hyperparathyroidism; a study of 25 cases. *Am. J. Path.*, 11: 1–72, 1935.
3. Möller, Heinrich. Zur Lehre der Epithelkörperchen. *Cor.-Bl. f. schweiz. Aerzte.*, 41: 578–586, 1911.
4. Gjestland, G. Ein Fall von Paralysis agitans mit bedeutender Vergrösserung der Glandulae parathyreoideae. *Ztschr. f. klin. Med.*, 76: 237–241, 1912.
5. Harbitz, Francis. On tumors of the parathyroid glands. *J. M. Research*, 32: 361–376, 1915.
6. Bergstrand, H. Parathyreoideastudien. II. Über Tumoren und hyperplastische Zustände der Nebenschilddrüsen. *Acta med. Scandinav.*, 54: 539–600, 1921.
7. Hoffheinz. Über Vergrösserungen der Epithelkörperchen bei Ostitis fibrosa und verwandten Krankheitsbildern. *Virchows Arch. f. path. Anat.*, 256: 705–735, 1925.
8. Paul, Fritz. Ostitis fibrosa generalisata, Epithelkörperchen und Nebennieren. *Beitr. z. path. Anat. u. z. allg. Path.*, 87: 503–525, 1931.
9. Bergstrand, Hilding. Ostitis fibrosa generalisata Recklinghausen mit pluriglandulärer Affektion der innersekretorischen Drüsen und röntgenologisch nachweisbarem Parathyreoideatumor. *Acta med. Scandinav.*, 76: 128–152, 1931.
10. Beyerinck, C. W. Quoted by Snapper, Isidore.[11]
11. Snapper, Isidore. Medical Clinics on Bone Diseases; A Text and Atlas. P. 225. New York, 1943. Interscience Publishers, Inc.
12. Hellström, J. Hyperparathyroidism and Ostitis fibrosa generalisata. *Acta chir. Scandinav.*, 69: 237–304, 1931.
13. Hellström, John and Wahlgren, Fredrik. Hyperparathyroidism. Clinical and pathologic observations of 12 cases. *Acta chir. Scandinav.*, 91: 472–498, 1944.
14. Hanke, Hans. Pathologische und theoretische Untersuchungen über Osteodystrophia fibrosa (von Recklinghausen) und ihre Beziehung zu Epithelkörperchentumoren. *Arch. f. klin. Chir.*, 172: 366–402, 1932–1933.
15. Churchill, E. D. The operative treatment of hyperparathyroidism. *Ann. Surg.*, 100: 606–610, 1934.
16. Capps, R. B. Multiple parathyroid tumors with massive mediastinal and subcutaneous hemorrhage; a case report. *Am. J. M. Sc.*, 188: 800–805, 1934.
17. Castleman, Benjamin and Mallory, T. B. Parathyroid hyperplasia in chronic renal insufficiency. *Am. J. Path.*, 13: 553–574, 1937.
18. Cope, Oliver. The surgery of subtotal parathyroidectomy. *New England J. Med.*, 213: 470–474, 1935.

19. Churchill, E. D. and Cope, Oliver. The surgical treatment of hyperparathyroidism; based on 30 cases confirmed by operation. *Ann. Surg.*, 104: 9–35, 1936.
20. Albright, Fuller, Sulkowitch, H. W. and Bloomberg, Esther. Hyperparathyroidism due to idiopathic hypertrophy (hyperplasia?) of parathyroid tissue; follow-up report of six cases. *Arch. Int. Med.*, 62: 199–215, 1938.
21. Cope, Oliver. Surgery of hyperparathyroidism: the occurrence of parathyroids in the anterior mediastinum and the division of the operation into two stages. *Ann. Surg.*, 114: 706–731, 1941.
22. Cope, Oliver. Hyperparathyroidism: the significance of generalized hyperplasia; report of the seventh case. *Clinics*, 1: 1,168–1,178, 1943.
23. Thyssen, J. Case of hyperparathyroidism and osteitis fibrosa with adenomatous hyperplasia of all parathyroid glands. *Ugesk. f. læger.*, 105: 869, 1943.
24. Flink, E. B. Hyperparathyroidism. *M. Clin. North America*, 29: 389–404, 1945.
25. Rogers, H. M. Parathyroid adenoma and hypertrophy of the parathyroid glands. *J. A. M. A.*, 130: 22–28, 1946.
26. Rogers, H. M., Keating, F. R., Jr., Morlock, C. G. and Barker, N. W. Primary hypertrophy and hyperplasia of the parathyroid glands associated with duodenal ulcer: report of an additional case with special reference to metabolic, gastrointestinal and vascular manifestations. *Arch. Int. Med.*, 79: 307–321, 1947.
27. Black, B. M. and Sprague, R. G. Hyperparathyroidism due to diffuse primary hypertrophy and hyperplasia of the parathyroid glands: report of case. *Proc. Staff Meet., Mayo Clin.*, 22: 73–80, 1947.
28. Pemberton, J. dej. and Keating, F. R., Jr. (Unpublished data.)
29. Albright, Fuller. The parathyroids—physiology and therapeutics. *J. A. M. A.*, 117: 527–533, 1941.
30. Gilmour, J. R. and Martin, W. J. Weight of parathyroid glands. *J. Path. & Bact.*, 44: 431–462, 1937.
31. Long, G. C. and Black, B. M. Metastatic hypernephroma of the thyroid. *Proc. Staff Meet., Mayo Clin.* 20: 43–48, 1945.
32. Wilder, R. M., Camp, J. D., Robertson, H. E. and Adams, Mildred: A fatal case of hyperparathyroidism, with report of necropsy. *Proc. Staff Meet., Mayo Clin.*, 7: 597–606, 1932.
33. Drake, T. G., Albright, Fuller and Castleman, Benjamin. Parathyroid hyperplasia in rabbits produced by parenteral phosphate administration. *J. Clin. Investigation*, 16: 203–206, 1937.
34. Pope, Alfred and Aub, J. C. The parathyroid glands and parathormone. *New England J. Med.*, 230: 698–707, 1944.
35. Lober, Paul, Hertzog, A. J. and Rice, C. O. Parathyroid adenoma, with uremia due to calcification of the kidneys. *Arch. Path.*, 41: 661–667, 1946.
36. Keating, F. R., Jr. and Cook, E. N. The recognition of primary hyperparathyroidism; an analysis of twenty-four cases. *J. A. M. A.*, 129: 994–1,002, 1945.

The Shoulder-Hand Syndrome*

Associated Painful Homolateral Disability of the Shoulder and Hand with Swelling and Atrophy of the Hand

OTTO STEINBROCKER, M.D.
NEW YORK, NEW YORK

THIS report is based on six patients, among over 200 cases of painful dysfunction of the shoulder, presenting the peculiar combination of painful shoulder disability with homolateral swelling of the hand. In five patients the swelling of the hand was followed by trophic changes. In almost every instance the condition had been diagnosed at some time or other as rheumatoid arthritis, usually of the atypical variety. Some of the patients had been treated with gold salts, radiation therapy and a variety of measures employed in rheumatoid disease. Other diagnoses were scleroderma, bursitis and periarthritis, infectious arthritis and scalenus anticus syndrome. Whether the clinical picture about to be described is merely symptomatic of a complicated form of fibrositis in the shoulder and neck region, some vascular or neurological disturbance, particularly a sympathetic neuropathy, remains unestablished. Nevertheless, owing to the distinctive diagnostic and prognostic features of this disorder it merits special emphasis, perhaps even classification as a separate entity.

As far as can be discerned from our small series, the condition goes through three stages of evolution: The first consists of a painful disability of the shoulder with generalized swelling and stiffness of the hand and fingers appearing with acute painful onset or developing insidiously over three to six months. (Fig. 1.) Either the shoulder or hand symptoms may arise first, followed by involvement of the other part, or both may be affected simultaneously and gradually. The next phase, during another three to six months, consists of gradual relief of pain and dysfunction noticeable at the shoulder, accompanied as a rule by resolution of the swelling of the hand. Stiffness and flexion deformity of the fingers, however, become more pronounced as the swelling is absorbed. (Fig. 3.) Osteoporosis is increasingly distinguishable in films of the hand and shoulder. (Fig. 2.) The third stage of the picture then follows as trophic changes in the hand become noticeable. Limited flexion and stiffness of the fingers remain troublesome. Contracture of flexor tendons, especially on the ulnar side, occurred in four of the patients. This disabling and disfiguring feature has lasted five years in one patient and is still present in another after seven years. (Fig. 4.) The symptoms and signs follow a rather typical pattern in their development, character and resolution, varying merely as to severity and duration in individual cases. In the mildest the whole clinical picture from onset to recovery took ten months; the most severe case after 7 years still exhibits partial, and possibly irreversible, disability of the shoulder and hand with contractures of three fingers.

* From the Arthritis Clinic and Medical Service, Bellevue Hospital, Fourth Division (N.Y.U.). Read in summary before the American Rheumatism Association, N.Y.C., May 24, 1946.

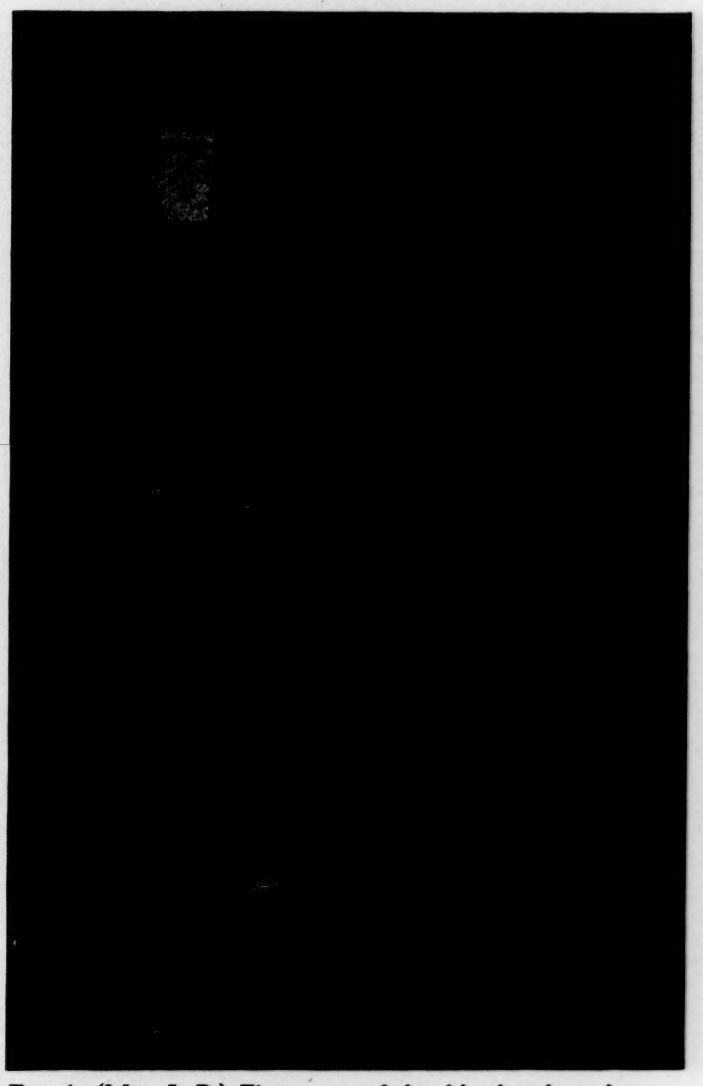


FIG. 1. (Mrs. I. B.) First stage of shoulder-hand syndrome: Diffuse swelling from wrist down over dorsum of hand and throughout the digits of three months' duration; associated shoulder pain and disability of six months' duration.

Shoulder discomfort and limited motion in all directions resemble the symptoms in periarthritis. Diffuse tenderness about the joint is elicited during the period of involvement. Swelling of the shoulder area was seen in only one of the cases. The swelling of the hand develops below the wrist, is uniform and generalized over the metacarpals and digits with little or no pitting. The hand may appear pinker than the opposite one and increased heat of the part may be demonstrated. Sometimes the swollen tissues are pale or cyanotic. Stiffness of the articulations persists throughout the clinical course. Widespread tenderness to palpation is found but is no greater about the joints. When atrophy occurs, it seems to be due to a more or less uniform shrinkage of subcutaneous tissue and muscle in the hand and fingers. Contractures appear to be tendinous. An antecedent history of infection or trauma was obtained in only one of the patients, who gave a story of a mild "sprain of the shoulder" before his

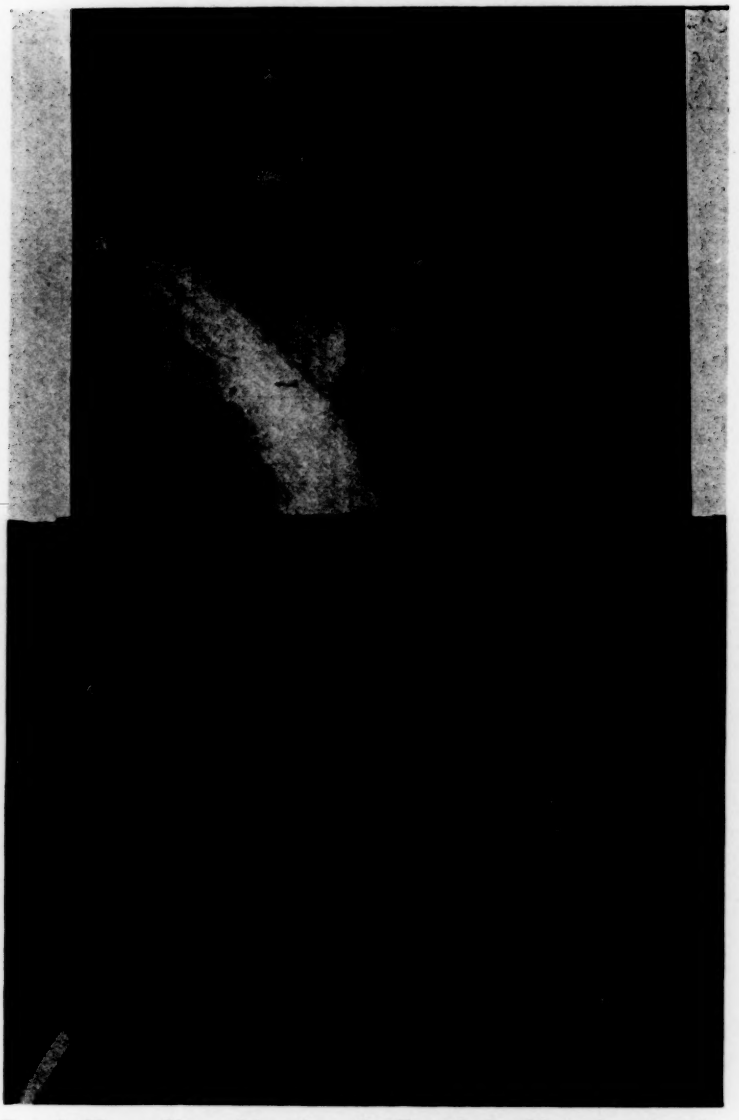


FIG. 2. X-ray films of hands and affected shoulder of patient in Figure 1 showing decalcification of wrist and hand and some osteoporosis at humeral head.

symptoms appeared. Five of the patients were under great emotional strain. Two showed moderate to severe osteoarthritis of the cervical spine. (Table I.)

Differential diagnosis requires exclusion of a number of similar conditions according to the stage of the disorder; most frequently atypical rheumatoid arthritis and, in the later phases, scalenus anticus syndrome and scleroderma. The only resemblance to the scalenus syndrome lies in the tenderness of the scalenus area, along with other points of soreness in the neck and shoulder and weakness of the grip. Injection of the scalenus anticus muscle with procaine proved ineffective. The possibility that the swelling of the hand represents compression of an anomalous subclavian vein running beneath the muscle, instead of over it, was not confirmed in one patient subjected to exploration.

The appearance of the hand in the shoulder-hand syndrome is only suggestive of rheumatoid arthritis. The swelling of the hand and digits is uniform, affecting all of

them diffusely, instead of being limited to the periarticular area of one or several joints as in rheumatoid disease. The tenderness to palpation also is generalized and is elicited equally anywhere on the hand. The persistent homolateral involvement of the shoulder and hand without symptoms in other joints or even on the other side of the body is unlike the behavior of rheumatoid arthritis. When seen during the most florid stage the sedimentation rate was elevated in one of the six cases.

A condition similar to this shoulder-hand disorder in almost every other detail, but usually affecting both hands in addition to one or both shoulders, has been described by Askey[1] and exhaustively by Johnson,[2] who termed the disorder post-infarction sclerodactylia. These authors, among others, have reported its appearance three to sixteen weeks after myocardial infarction, or in association with symptoms of angina pectoris. Unfortunately, the electrocardiograms of two of our patients seen eight and nine years ago are not available. All patients in our series, however, were free from any clinical signs of cardiac disease and gave no history of angina or infarction. Among the post-infarction patients reported in the literature, males predominated, while five of our six subjects were females. The thirty-nine patients of Johnson showed bilateral hand involvement. Some of the trophic terminal changes described and illustrated in post-infarction sclerodactylia were unlike those seen in our cases.

The patients in this series developed no cardiac symptoms even during the course of extensive follow-up. The possibility of a preceding infarction cannot be excluded because the patients were not seen and electrocardiographic and clinical study was not carried out until what would have been a long period after the initial coronary occlusion. It is conceivable but unlikely that six consecutive patients would be seen with silent infarctions without a history of some symptoms or of anginal complaints. Even from the meager information supplied by so few cases, one cannot help suspect under the circumstances that the shoulder-hand disorder may develop also in patients free from coronary disease. Its position in this respect may well be analogous to painful disability or periarthritis of the shoulder, as well as Dupuytren's contracture. Each of these has been reported in a relatively high percentage of patients with angina pectoris or myocardial infarction. Yet they occur frequently in otherwise healthy individuals.

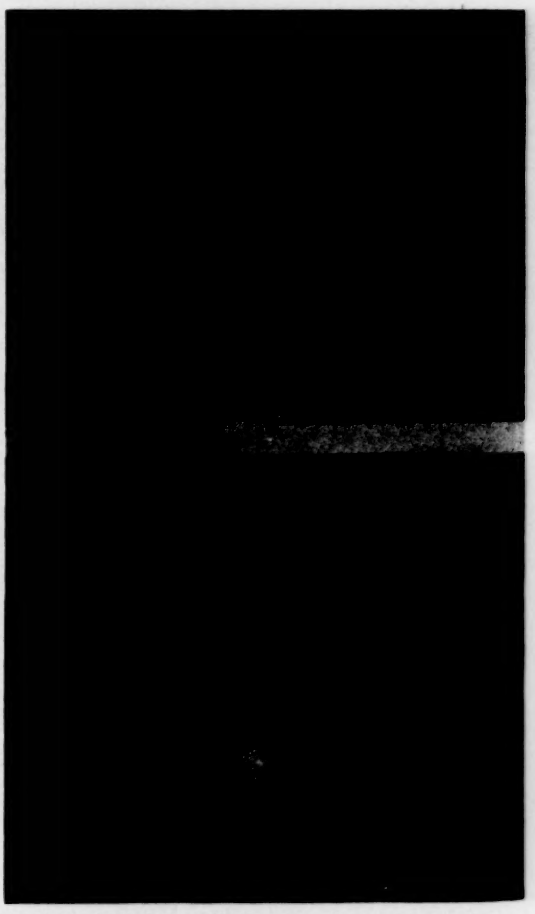


FIG. 3. (Mrs. J. S.) Intermediate stage of the disorder of eight months' duration; swelling of hand almost gone, flexion posture of fingers definite, trophic changes becoming noticeable; shoulder disability still present. Flexion deformity of digits has lasted five years; shoulder function recovered about three months after this photograph was taken.

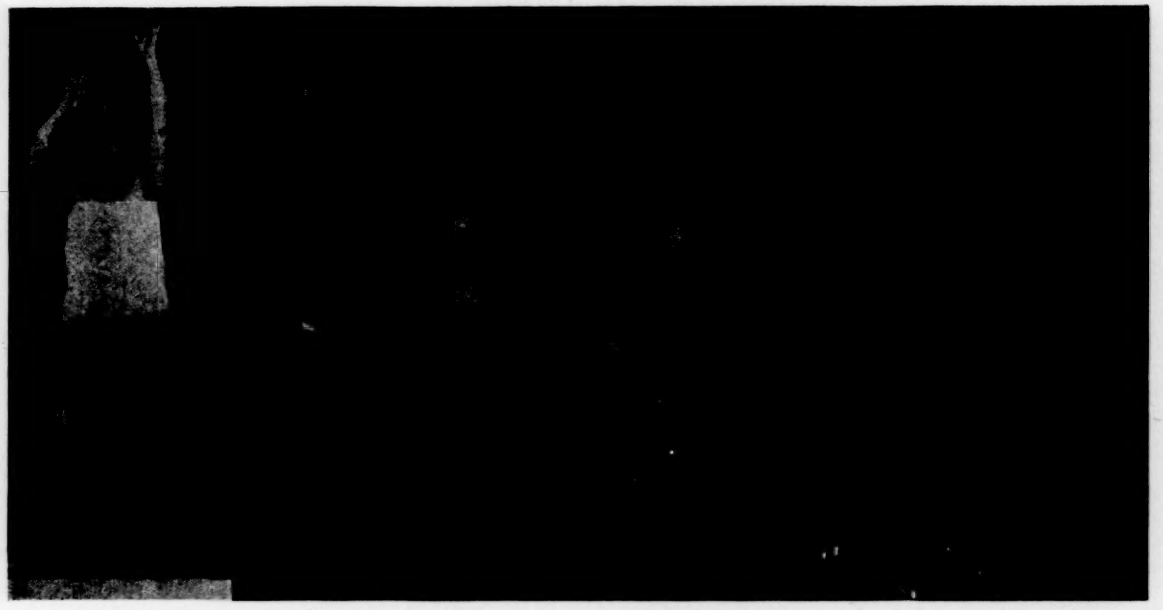


FIG. 4. (Mrs. M. B.) Terminal stage with contractures of fingers and residual shoulder disability seven years after onset; observed throughout typical stages of clinical picture.

In our cases of the shoulder-hand syndrome recovery occurred spontaneously by slow stages. The shoulder discomfort and disability subsided within three to twelve months. The swelling of the hand resolved within a similar period. The trophic changes of the hand were more slowly replaced by normal appearance and function after approximately two years and four years in two patients. After seven years the changes still persist in another. One patient has been under observation for less than a year and has developed atrophy in the last two months. In the mildest case there was only muscle weakness which seems to have improved without any residual atrophy. One patient did not remain under observation after the initial study.

Acute bone atrophy, causalgia, post-traumatic osteoporosis, reflex dystrophy or Sudek's atrophy is suggested by this clinical picture.[3–6] The signs and osteoporosis were similar in many ways in our cases but they developed much more insidiously than in Sudek's atrophy. The trauma or suppuration usually preceding the syndrome described by Sudek was lacking completely in five of our 6 patients. It is possible that

TABLE I

Patient	Age	Sex	Occupation	Side Affected	History of Trauma	Cardiac or Coronary History	ECG	E.S.R.	Changes Cervical Spine (Films)	Result	Duration of Hand Disability
A. J.	55	F	Housewife	R	0	0	Normal	Normal	Moderate	Recovery	2 yr.
J. S.	45	F	Housewife	L	0	0	No record	Normal	0	Recovery	5 yr.
M. B.	58	F	Housewife	R	0	0	Normal	52 m.m.	Moderate	Contracted 3, 4, 5 digits still present; slight residual at shoulder	7 yr.
M. R.	52	F	Housewife	R	0	0	No record	Normal	0	Unknown	Unknown
J. P.	52	M	Metal plater	R	"Sprain" of shoulder	0	Normal	Normal	0	Recovery; slight weakness hand muscles	10 mo.
I. B.	49	F	Housewife	L	0	0	0	Normal	0	Recovery; slight weakness hand muscles	18 mo.

some minor trauma or torsion may have occurred without our patients' noticing it, as surgeons have postulated in similar clinical pictures. It is just as likely that such an assumption merely leads us away from other causes ultimately to be established.

A group of fourteen patients presenting swelling and atrophy of the hand, in many respects like our cases, has been reported by Oppenheimer.[8] Apparently his patients did not present the associated shoulder disability. In all of the cases the upper cervical spine showed intraforaminal constriction by bony spurs to which the author attributed the clinical picture. Cervical osteoarthritic changes were found in only two of our patients. It is possible the special radiographic technic employed by him would increase the number showing these peculiarities. The clinical course described differs in many ways from that of our patients.

From this small series it appears that the shoulder-hand syndrome observed in the majority of our cases resembles in some features "post-infarction sclerodactylia," Sudek's atrophy, and the swollen atrophic hand with cervical osteoarthritis described by Oppenheimer. Yet it differs sufficiently to suggest a distinctive syndrome. These disorders probably have a common relationship in the neurovascular reflex mechanism which seems to underlie all of them. They may, therefore, represent variations of sympathetic and spinal reflex reactions to different etiologic factors: trauma, myocardial infarction, intraforaminal constriction by bony spurs and the "idiopathic" group, as in our patients, in which the cause remains to be established.

Treatment of the shoulder-hand syndrome has not been extensive enough so far to permit of definite conclusions. Diathermy to the cervical spine and deep x-ray therapy have been recommended by others.[8,9] In post-traumatic and other reflex dystrophies favorable results have been reported from paravertebral sympathetic nerve block and, in unresponsive cases, sympathetic nerve section.[4–7]

SUMMARY

In the six patients described here the shoulder-hand syndrome proved to be a painful, disabling condition leading in some instances to long standing, and in one case possibly permanent, trophic changes of the hand. Its appearance requires thorough study of the patient and evaluation of the cardiac status. For the present it must be regarded in cases like ours as a non-traumatic, non-cardiac, idiopathic disorder acting through a disturbed neurovascular mechanism. If the differentiation of this clinical picture serves only to avoid unsuitable therapy and to provide a better insight into the prognosis, its recognition as a special entity is justified.

REFERENCES

1. Askey, J. M. The syndrome of painful disability of the shoulder and hand complicating coronary occlusion. *Am. Heart J.*, 22: 1, 1941.
2. Johnson, A. C. Disabling changes in the hands resembling sclerodactylia following myocardial infarction. *Ann. Int. Med.*, 19: 433, 1943.
3. Sudek, P. Die trophische Extremitätenstörung durch periphere (infectiöse und traumatische) Reize. *Arch. klin. Chir.*, 62: 147, 1900.
4. De Takats, G. and Miller, D. S. Post-traumatic dystrophy of the extremities. *Arch. Surg.*, 46: 469, 1943; *Surg., Gynec. & Obst.*, 75: 558, 1942.
5. Evans, J. A. Reflex sympathetic dystrophy. *Surg., Gynec. & Obst.*, 82: 36, 1946.
6. Leriche, R. The Surgery of Pain. Baltimore, 1939. Williams & Wilkins.
7. White, J. C. and Smithwick, R. H. The Autonomic Nervous System. New York, 1941. Macmillan.
8. Oppenheimer, A. The swollen atrophic hand. *Surg., Gynec. & Obst.*, 67: 446, 1938.
9. Numford, B. Roentgen therapy in acute osteoporosis; new type of treatment. *J. Bone & Joint Surg.*, 20: 949, 1938.

The Altered Response of Human Beings to the Intramuscular Administration of Typhoid Vaccine during Massive Salicylate Therapy*

B. V. JAGER, M.D. *and* MARGARET NICKERSON
SALT LAKE CITY, UTAH

THE parenteral administration of typhoid vaccine to normal subjects usually results in the development of circulating antibodies to this organism. In addition, this toxic bacterial protein causes a transient rise in the plasma fibrinogen, the erythrocyte sedimentation rate and total leukocyte count as well as a transient decrease in total lymphocytes. Often there are local reactions at the sites of injection. Systemic reactions also may occur. A rise in serum "gamma globulin" as determined chemically follows administration of the vaccine. In order to determine what modifying influences might result during salicylate medication, we have studied the effects of the injection of typhoid vaccine in a control group of eighteen adults as contrasted with fourteen patients receiving massive doses of salicylates. In all instances measurements of the formation of antibody to the typhoid organisms were performed. In several subjects in the group, additional studies included the frequent determinations of total serum protein, serum albumin, serum globulin, plasma fibrinogen, "gamma globulin," volume of packed red cells, erythrocyte sedimentation rate and total leukocyte and differential leukocyte count. From these measurements, it was hoped to gain further information as to the mode of action of salicylates.

MATERIAL AND METHODS

The control group of eighteen adults, eleven males and seven females, consisted of thirteen healthy hospital personnel, two patients with multiple sclerosis, one patient with arteriosclerotic heart disease and two patients with active rheumatic fever. Their ages ranged from twenty-one to forty-eight years. Nine of this group gave a history of previous injections of typhoid vaccine within five years prior to the present study while the other nine subjects denied having received typhoid vaccine or having had typhoid fever.

In the group of fourteen individuals who were receiving massive salicylate therapy at the time of administration of the vaccine, there were nine females and five males whose ages ranged from nineteen to forty-one years. Eight of these patients had acute rheumatic fever; three, rheumatoid arthritis; two, dermatomyositis; and one was thought to have periarteritis nodosa. Nine of these patients had been immunized previously within the past five years with typhoid vaccine. In the entire group of fourteen subjects, salicylate medication had been administered for 7 to 132 days before the injections of typhoid vaccine for the present study. The plasma salicylate levels in the week preceding and for two weeks after administration of the antigen were main-

* From the Department of Medicine, University of Utah School of Medicine, Salt Lake City, Utah. Aided in part by grants from the Physicians' Research Fund of the University of Utah School of Medicine and the Fluid Research Fund of the Rockefeller Foundation.

tained between 300 and 410 micrograms per cc. of plasma in twelve of the fourteen patients and between 200 and 300 in the other two patients. Salicylate therapy was discontinued at intervals varying from sixteen to seventy days after immunization, the average duration of salicylate medication being thirty-five days after the injections of vaccine.

The vaccine employed was stated to contain one billion typhoid and 500 million paratyphoid A and paratyphoid B organisms per cc. The protein content of the washed bacterial suspensions varied from 80 to 110 micrograms of nitrogen per cc. Each subject received 1 cc. of this vaccine intramuscularly in the deltoid area. A second injection of 1 cc. was administered forty-eight hours later in the same area. Each injection was made in the evening.

The typhoid antibodies were measured with twofold dilutions of serum in saline, beginning with a dilution of 1:20 so that, after adding an equal volume of organisms the final volume of the initial dilution was 1:40. The typhoid H antigen was prepared by treating a suspension of bacteria with 0.2 per cent formalin while the O antigen was prepared by treatment of live organisms with ethyl alcohol. The original typhoid H antigen showed a definite agglutination in stock rabbit antiserum which was diluted to 1:5,120 but no visible agglutination in the next dilution. The original O antigen showed definite agglutination in a 1:640 dilution of the antiserum but not in antiserum diluted to 1:1,280. Each subsequent lot of antigen was tested with this same stock rabbit antiserum. No new antigens were employed which differed from the original antigens by more than one dilution in their sensitivity to agglutination in the stock rabbit antiserum.

The serial dilutions of the sera to be examined plus the H or O antigen were placed in a water bath for five hours at 56°C. The H antibodies were read immediately after incubation while the O antibodies were read after subsequent refrigeration at 4°C. for eighteen hours. In a few instances, the same sample of human serum was checked after storage to determine the relative constancy of the antibody titer with different lots of antigens. The antibody titers for H antigen did not vary more than one dilution. The H antibodies are detected readily. The O antibodies, however, are more difficult to read and less accuracy was possible in their measurement. Following the administration of vaccine, antibody titers for sera were determined twice during the first week, thrice during the second week and, thereafter, once a week for many weeks. For convenience the antibody titers are expressed as the reciprocals of the saline dilutions of the sera. Arbitrarily we have considered sera with less antibody than 1:40 as containing no antibodies.

In nearly all instances blood specimens for protein studies and for determination of erythrocyte sedimentation rate, leukocyte count and differential leukocyte count were drawn between 10 and 11 A.M. At least two samples of blood were examined in the two weeks interval prior to the administration of the vaccine. For this study, blood was withdrawn daily from the subjects for six days following injection of the vaccine, three times during the second week, twice during the third week and thereafter weekly for periods of three to twelve weeks. Since the typhoid vaccine was administered in the evening, the initial blood specimens were obtained about 18 hours later. All glassware was chemically clean. Salicylate levels of the plasma were determined thrice weekly by the method of Brodie and coworkers.[1] All protein measurements were made with the biuret method of Kingsley.[2] Lipemic sera were treated with ethyl ether before making a colorimeter reading. The plasma

fibrinogen was determined by the method of Cullen and Van Slyke[3] by measuring the protein content of the clot of oxalated plasma. This was prepared by adding 1 cc. of plasma to 28 cc. of normal saline and 1 cc. of 0.1 M calcium chloride. The serum albumin and total globulin determinations were made with 23 per cent sodium sulfate, using the Howe method.[4] The initial two-fifths of the filtrate was discarded as recommended by Gutman and coworkers.[5] The "gamma globulin" fraction was obtained by adding saturated ammonium sulfate to undiluted serum to a saturation of 33 per cent. This was accomplished under controlled pH determinations (measured with glass electrode) and with care as to the rapidity of precipitation. This method has been described briefly elsewhere[6] and will be described in detail later.[7] It is sufficient to state here that the 33 per cent ammonium sulfate precipitate of human sera contains certain antibodies present in Fraction II of Cohn (electrophoretically Cohn's Fraction II contains 98 per cent gamma globulin) while it contains no significant amount of other antibodies (typhoid O and isoagglutinins) present in Cohn's Fraction III-1 (electrophoretically this fraction of Cohn contains 3 per cent alpha globulin, 70 per cent beta globulin and 25 per cent gamma globulin).[8] Moreover, the "gamma globulin" fraction as determined chemically with ammonium sulfate is found to be greatly increased in certain diseases in which elevated gamma globulin values have been observed by electrophoretic studies. The sedimentation rate of whole blood and the volume of packed red cells were determined by the method of Wintrobe.[9] The sedimentation rates were not corrected for the presence of anemia for this was not present to any great extent in any subject used in this study. The total leukocyte counts were determined by counting four large squares of a standard counting chamber. Differential leukocyte counts were performed by random selection of 100 leukocytes on blood smears drawn on glass cover slips and stained by Wright's method.

TABLE I

STATISTICAL EVALUATION OF VARIOUS PROCEDURES AS CARRIED OUT IN NORMAL PERSONS

Blood Constituent	No. Persons	No. Determinations	Median	Range of 90% of Values	Total Range	Standard Deviation Due to Method	Possible Error of Method in Per Cent
Total Protein Gm. per cent	29	218	6.94	6.20–7.59	5.60–7.99	±0.033 Gm.	±0.48%
Albumin Gm. per cent	21	166	4.43	4.00–4.89	3.50–5.49	±0.029 Gm.	±0.65%
Total Globulin Gm. per cent	22	161	2.59	1.80–2.99	1.20–3.59		
Albumin: Total Globulin	22	162	1.85	1.40–2.39	1.20–3.59		
"Gamma" Globulin Mg. per cent	32	168	788	550–1049	500–1149	±0.021 Gm.	±2.66%
"Gamma" Glob.: Total Prot.	33	165	11.4	8.5–13.9	7.0 –14.9		
Fibrinogen Mg. per cent	17	143	262	200– 329	170– 349	±0.009 Gm.	±3.44%
Sedimentation Rate Mm. per hour	13	118	6.4	0–14.9	0–21.9		
Hematocrit Reading Cc. per cent	15	179	46.5	42.0–52.9	38.0–54.9		
White Blood Count cells per c. mm	13	126	6882	5000–9999	4000–11999		
Lymphocytes cells per c. mm.	8	54	2480	1600–3999	1200– 4399		

Standard deviation due to method calculated from triplicate determinations of serum from ten normal individuals.

In Table I are given normal values for these procedures in our hands, using the methods mentioned above. A large number of determinations have been made on a relatively small number of controls. This was done to determine the constancy of the

various constituents from day to day in a given individual.

The addition *in vitro* of sodium salicylate in concentrations of 1,000 micrograms per cc. (expressed as salicylic acid) to whole serum or plasma and incubation for eighteen hours at 37°c. using sterile technic, failed to demonstrate that this amount of salicylate modified in any way the determination of antibody titer, plasma fibrinogen, total serum protein, albumin, globulin, or the serum "gamma globulin" content as compared with serum or plasma incubated without salicylate.

RESULTS

Both the control subjects and the patients receiving sodium salicylate were subdivided into those who gave a history of having had previous typhoid vaccine and those who never had received this vaccine. In the latter group, failure to recollect vaccine administration previously, and the possibility of asymptomatic or unrecognized typhoid infection previously, could not be excluded.

In the control subjects the initial intramuscular injection of typhoid vaccine usually was attended by a moderately severe local inflammatory reaction characterized by redness, heat and local discomfort. With the second injection forty-eight hours later, the local reactions invariably were less severe than after the initial injection. No distinct difference in intensity of local reaction could be detected in the nine control subjects who had not been immunized previously (Group I) as compared with the nine who had been immunized previously (Group II). In one of nine members of Group I and in seven of nine subjects in Group II, there occurred systemic reactions following the first or second injection. These consisted of headache, malaise, anorexia and fever usually lasting only twenty-four hours. In three of the ten subjects with systemic reactions the temperature exceeded 103°F. Systemic reactions were more frequent after the second injection than after the first. When systemic reactions followed the first injection, they became intensified after the second injection.

By contrast, local reactions in the patients receiving salicylate medication were mild and short lived. Only three of these fourteen patients developed significant erythema and heat at the site of injection. No systemic reaction followed administration of the vaccine in any of the fourteen patients who were receiving salicylates. This included nine patients who had been immunized previously.

The antibody response to the H antigen of the typhoid organism in the control subjects and in the patients receiving sodium salicylate showed considerable individual variation as regards time of appearance of antibodies, maximal antibody titers and duration of circulating antibodies. In the control subjects the initial rise in antibody titer usually appeared about the fifth day after injection of vaccine, reaching a maximal titer at the end of one week, gradually falling thereafter. As illustrated in Figure 1 and in Table II, the H antibody titer (mean values) rose much higher in those control subjects who had been immunized previously with typhoid vaccine (Group II) than in those who had not (Group I). Two subjects without previous immunization failed to develop any H antibodies with this program of immunization. In the nine controls who previously had been given typhoid vaccine, three had residual antibody titers of 40 to 160 at the time this experiment was begun. In no member of this previously immunized group was an immediate increase of antibody to the H antigen observed in the specimen taken eighteen hours after the initial injection. All nine subjects in the group with a history of previous immunization developed significantly elevated titers

of antibodies to H antigen following vaccination. (Table II.)

Antibody titers to H antigen in the patients receiving large doses of salicylates were much lower. (Fig. 1, Table II.) In those patients receiving salicylates who gave typhoid vaccine. In the entire group of nine patients (Group IV) the rise in antibody titer to H antigen was much less than that observed in the group of nine control subjects (Group II) who had been immunized previously. Since the differences in the mean

TABLE II

NUMBER OF INSTANCES IN WHICH VARIOUS ANTIBODY TITERS WERE OBSERVED IN CONTROL SUBJECTS AND IN PATIENTS RECEIVING SALICYLATES

Group	No. Subjects	Antibody Titer to Typhi H								No Antibodies	Titer before Injection		
		40	80	160	320	640	1280	2560	5120		40	80	160
I	9	7	7	7	5	4	2	0	0	2	0	0	0
II	9	9	9	9	9	9	5	3	1	0	3	2	1
III	5	1	1	0	0	0	0	0	0	4	0	0	0
IV	9	8	8	4	2	2	0	0	0	1	3	2	1

Group	No. Subjects	Antibody Titer to Typhi O								No Antibodies	Titer before Injection		
		40	80	160	320	640	1280	2560	5120		40	80	160
I	7	5	4	3	2	1	1	0	0	2	0	0	0
II	8	8	7	4	3	3	0	0	0	0	2	0	0
III	3	2	1	1	0	0	0	0	0	1	0	0	0
IV	5	5	4	3	0	0	0	0	0	0	2	0	0

Group I = Control subjects not previously immunized.
Group II = Control subjects previously immunized.
Group III = Patients receiving salicylates not previously immunized.
Group IV = Patients receiving salicylates previously immunized.

no history of previous antigen administration (Group III) none had antibodies prior to injection of the typhoid vaccine. Four of the five failed to develop any circulating antibody (less than forty) to the H antigen although two of these did develop low antibody titers to the O antigen. In the nine patients receiving salicylate medication who gave a history of previous vaccine administration (Group IV), three had antibody titers of 40 to 160 prior to the new injections of this substance. This appears significant inasmuch as these three patients had been receiving large doses of salicylates for at least four weeks before their injections of titers of antibody content in these two groups exceeded two dilutions, this finding appears significant. As we have indicated earlier, the expected error in the method does not exceed one dilution.

Greater individual variation in antibody response to the O antigen than the H antigen was observed in all groups. Frequently this antibody appeared several days earlier than the H antibody and usually disappeared more rapidly. In those controls who had been immunized previously, an apparent anamnestic response was encountered in three of the eight subjects in whom determinations of O antibody titer were made 18

hours after the initial injection of vaccine. This consisted of a rise in the antibody titer to values of 40 to 160. While the number of observations is small, the results as indicated in Table 2 suggest that some depression of O antibody formation occurred in the patients receiving salicylate medication as opposed to the controls.

During the course of salicylate therapy additional typhoid vaccine (1 cc. intramuscularly) was administered to three patients (Group III, two patients; Group IV, 1 patient) in whom the antibody response to the two injections of vaccine three to six weeks previously had been poor. In the two patients from Group III, a rise in antibodies to H antigen occurred after this new injection. However, the maximal titer following the new injection still was less than that observed in the control group to whom only two injections had been given. In the subject from Group IV, the rise in antibody titer following the new injection was slight and transient in character.

Three patients in Group III and two patients in Group IV received an additional 1 cc. of typhoid vaccine intramuscularly one to four weeks after discontinuation of salicylate medication and two to ten weeks after the two previous injections had been given. In all five a rise in antibody titer occurred after the new injection and in four this reached a maximal titer which was above that encountered following the two injections which were given during the course of salicylate therapy. In one patient, however, the rise in antibody titer to H antigen was very slight with this new injection. Previously this patient had developed no antibodies to the H antigen.

A few additional immunologic studies have been made. In three patients in whom initially there was a high antifibrinolysin content in the serum during active rheumatic fever, no apparent reduction in titer occurred during a prolonged course of salicylate therapy during which high plasma salicylate levels were maintained. The antifibrinolysin content of serum was performed by a slight modification of the method of Tillett.[10] In two patients in whom Dick and Schick tests were negative prior to

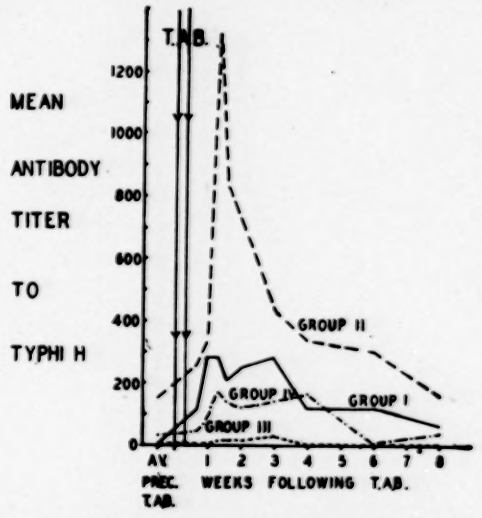


FIG. 1. Group I comprises nine control subjects without a history of previous administration of vaccine. Group II consists of nine control subjects who had been immunized previously with typhoid vaccine. Group III consists of five patients, not previously immunized, who were receiving large doses of salicylates while Group IV is composed of nine patients receiving salicylate medication in whom previous immunization had been carried out. Note the striking difference in antibody titer in Group II as compared with Group IV. "Av. Prec. T.A.B." refers to the average titer of two determinations made prior to injection of vaccine. "T.A.B." refers to the vaccine which consists of typhoid, paratyphoid A and paratyphoid B organisms.

salicylate therapy, repetition of these tests during the third or fourth week of salicylate medication still resulted in negative tests.

In a small group of controls and of patients receiving salicylate medication, we have determined the total leukocyte count and the absolute numbers of lymphocytes per c. mm. daily for six days after injection and two to three times per week thereafter

for two subsequent weeks. Since no apparent differences in the behavior of the total leukocyte and lymphocyte counts were observed between those subjects who had been previously immunized and those who had not, we have not separated these groups.

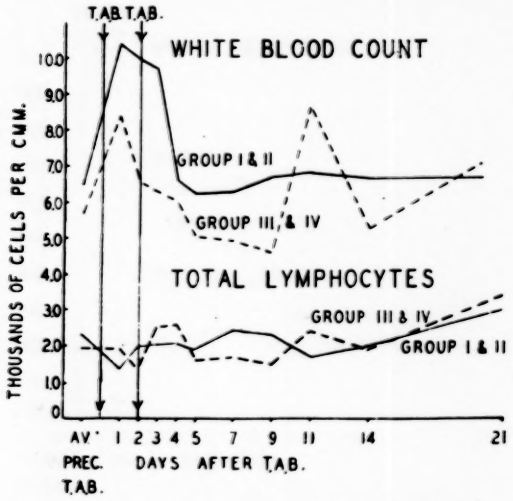


FIG. 2. The mean values for total leukocyte count and total number of lymphocytes per c.mm. in control subjects (Groups I and II) and in patients receiving salicylate medication (Groups III and IV) after administration of typhoid vaccine. Note the apparent greater leukocyte response in the control subjects as opposed to those receiving salicylate following injection of vaccine. It is uncertain whether the difference in the degree of reduction in numbers of lymphocytes in these two series is significant. (For explanation of groups, see Figure 1.)

Total leukocyte counts were followed in eight controls and in four patients receiving salicylate medication following typhoid vaccine. As is indicated in Figure 2, there occurred a moderate rise in the leukocyte count eighteen hours after the initial injection with no further rise following the second injection. The leukocyte count returned to its original level by the fourth day. By way of contrast, the leukocyte rise in the four patients receiving salicylate medication was smaller.

In six controls and in four patients receiving salicylates, the administration of typhoid vaccine was followed by a decrease in the absolute numbers of lymphocytes per c. mm. following the initial injection of typhoid vaccine. The reduction in lymphocytes was maximal at eighteen hours after the initial injection in the control group and eighteen hours after the second injection in the patients receiving salicylates. The rise in the total leukocyte count at a time when the lymphocyte count was decreasing was attributable to an increased number of granulocytes.

In nine control subjects and in seven patients receiving salicylate medication, we have made simultaneous determinations of the plasma fibrinogen and the erythrocyte sedimentation rate following administration of typhoid vaccine. No differences were noted in the subjects who had been immunized previously as opposed to those who were immunized for the first time. In the control group the rise in plasma fibrinogen was maximal thirty-six hours after the first injection and showed no further rise following the second injection. The fibrinogen returned to normal ranges within five days after the initial injection. No rise in plasma fibrinogen occurred in the patients receiving salicylates following administration of the typhoid organisms. (Fig. 3.)

The erythrocyte sedimentation rate in the control group showed a maximal rise on the third day after the initial injection and fell to the initial level over a period of eleven days. (Fig. 3.) It is apparent that the erythrocyte sedimentation rate lagged behind the plasma fibrinogen in the time required to attain the peak value as well as in the time taken to return to normal.

As is illustrated in Figure 3, the mean value for plasma fibrinogen prior to injection was slightly higher in the patients receiving salicylate medication whereas the mean erythrocyte sedimentation rate was considerably higher in those patients receiving salicylate medication than in the

controls. Actually the mean value in the patients receiving salicylate medication distorts the truth inasmuch as five of the nine patients receiving salicylate medication had initial erythrocyte sedimentation rate and plasma fibrinogen values as low as the initial values of the control subjects. In these five patients with normal values as in the four others in whom moderate elevation of fibrinogen and erythrocyte sedimentation rate occurred, there was no increase after administration of the vaccine.

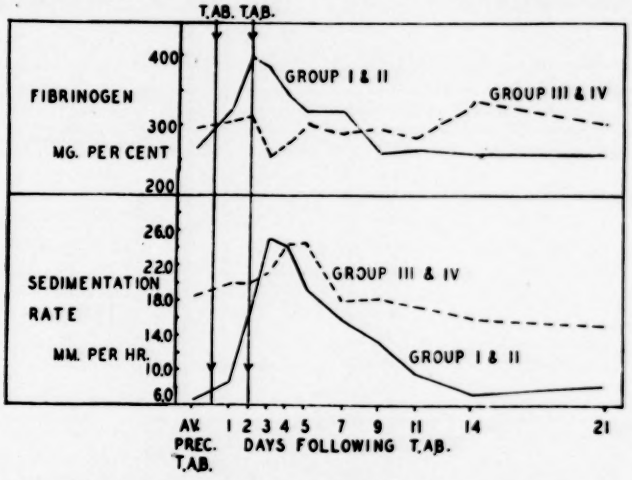


FIG. 3. Mean values for plasma fibrinogen and erythrocyte sedimentation rate in nine control subjects of Groups I and II, and in seven patients receiving salicylate medication in Groups III and IV, following administration of typhoid vaccine. Note the greater increase in plasma fibrinogen and in erythrocyte sedimentation rate in the control subjects.

In the control group, a slight delayed decrease in the volume of packed red cells occurred after administration of vaccine. In the group receiving salicylates the hematocrit readings were not constantly depressed and showed no distinct trend.

The total protein, albumin, globulin and "gamma globulin" of the serum were determined at frequent intervals after injections of typhoid vaccine in ten control subjects (five of Group I; five of Group II) and in eight patients receiving salicylates (three of Group III and five of Group IV). No consistent changes were observed in the total serum protein, serum albumin or total serum globulin after the typhoid vaccine. The serum "gamma globulin," however, did increase following the first injection of typhoid vaccine in the control subjects. It returned to normal within seventy-two hours after the first injection. A secondary rise in this fraction was noted again from seven to nine days after the initial administration of typhoid vaccine. (Fig. 4.) In the patients receiving salicylate medication, no immediate or delayed rise in the "gamma globulin" occurred.

In Figure 5 we have depicted the variations in the various components as determined in ten healthy adults. In this group, blood specimens were taken once each week and the mean values for each week are indicated in the chart. It is apparent that the mean variations observed in this control group were much less than the changes occurring in the control subjects who received typhoid vaccine. In addition, we now have followed these various protein constituents

at weekly intervals in twenty normal individuals for three months and have observed no variation comparable to that observed in the control subjects receiving typhoid vaccine. The same finding obtained for five control subjects in whom these determinations were made daily for six days.

by suitable parenteral routes in relatively large doses.

It seems reasonable to ascribe to the toxic action of the bacterial proteins, the inflammatory reaction observed at the site of injection. Why there is a less marked local reaction to a second injection of equal size

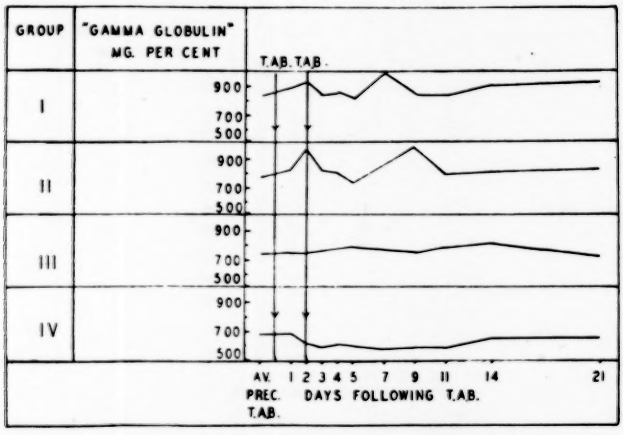


FIG. 4. Mean values for serum "gamma globulin" in ten control subjects from Groups I and II and in eight patients receiving salicylates in Groups III and IV after injections of vaccine. Note the immediate (second day) and delayed (sixth to tenth day) rises in "gamma globulin" in the control subjects after vaccination as opposed to the relatively slight change occurring in the patients receiving salicylate medication. (For explanation of groups, see Figure 1.)

COMMENTS

Before discussing the changes observed in the patients who received salicylates, it is important to consider the possible factors involved in the production of the changes that were observed after injection of typhoid organisms in the control subjects. The vaccine employed, which is a mixture of antigenic proteins, leads to the formation of specific antibodies. In addition, the vaccine contains bacterial proteins which may give rise to symptoms of sensitization in subjects who have received this substance previously. Finally, the bacterial proteins are toxic agents which, apart from any process of immunization or sensitization, produce local and systemic reactions when administered forty-eight hours later is not clear. In part the systemic reaction may be due to absorption of toxic proteins although, as we have indicated, systemic reactions usually occurred only in those individuals who had received this vaccine at an earlier date. In individuals in whom typhoid vaccine is administered intravenously, febrile reactions and systemic symptoms occur regularly. A rise in the plasma fibrinogen and in the erythrocyte sedimentation rate which we observed in the control subjects after the injections of the typhoid organisms also has been reported by Ham.[11] The increase in plasma fibrinogen is probably the most important factor in the production of an elevated erythrocyte sedimentation rate.[11,12,13,14]

However, as is illustrated in Figure 3, the increase in plasma fibrinogen alone does not explain entirely the observed elevation of the erythrocyte sedimentation rate in our cases since the elevation persisted after the plasma fibrinogen returned to normal. Contributing to the production of an elevated erythrocyte sedimentation rate, apart from anemia, are increases in the globulin or lipid content of the plasma[11,12] and possibly other changes in plasma constituents.

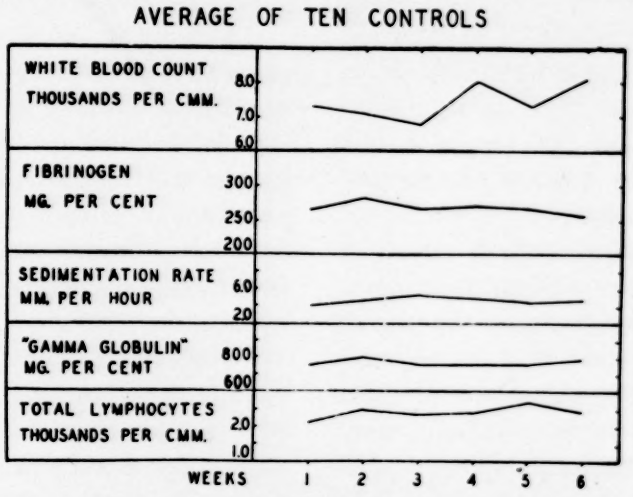


FIG. 5. Mean values for plasma fibrinogen, erythrocyte sedimentation rate, serum "gamma globulin," total leukocyte count and total lymphocyte count per c.mm. in ten control subjects. Each constituent was determined once weekly in each subject for six weeks. Note the relative constancy of these mean determinations from week to week.

Favorite and Morgan,[15] who injected a purified somatic antigen of the typhoid bacillus intravenously into man and rabbits, observed a rapid rise in the total leukocyte count and in the numbers of granulocytes following the injection. It appears likely that the similar response which we observed after injection of typhoid vaccine intramuscularly, resulted from the toxic action of bacterial proteins.

The possible rôle of bacterial sensitization such as might have resulted from previous injections of the typhoid vaccine, can be considered only by contrasting the control group of nine patients who have no history of immunization with the other nine controls who had been immunized previously. Strikingly different was the incidence of systemic manifestations; these were observed in only one of nine of the previously non-immunized controls but were observed in seven of nine who had been immunized previously. The only other significant variation between these two control groups was the higher antibody titer in the sera of the previously immunized subjects after readministration of the vaccine.

Before considering the changes observed in the "gamma globulin," lymphocyte counts and antibody titers of the control subjects, it is useful to recall current concepts about the interrelation of these components. Evidence indicates that antibodies are formed in the lymphocytes of lymphoid tissues.[16,17,18] Antibodies present in blood are largely contained in the gamma globulin fraction although some are included in the beta globulin fraction as determined electrophoretically.[8] It has been demonstrated that normal lympho-

cytes contain gamma globulin.[19,20] White and Dougherty[19] reported that extracts of lymphoid cells from immunized animals contained a striking increase in gamma globulin. These investigators also have shown that adrenal cortical steroids when administered to animals, result in rapid depletion of lymphocytes in lymphoid tissue and in decreased numbers of circulating lymphocytes.[21] This is accompanied by a prompt increase in the total protein and gamma globulin fraction of serum.[19] The stimulus for increased release of adrenal cortical steroids is initiated by adrenotrophic hormone which, when administered parenterally, produces changes comparable to those observed after injections of adrenal cortical steroids.[19] Moreover, various toxic chemical reagents and even injection of sheep cells into rabbits may give rise to pituitary-adrenal cortical stimulation as evidenced by a lymphopenia following injections of these substances.[22] The cumulated evidence thus indicates that the lymphocytes are an important source for gamma globulin synthesis (including antibodies) and release of this protein fraction from the lymphoid tissue into the circulation is controlled in part, at least, by pituitary-adrenal cortical stimulation. After a single injection of either adrenal cortical steroids or adrenotrophic hormone, the lymphopenia, depletion of lymphoid tissue, increase in gamma globulin and in total serum protein is transient, the maximal effect occurring before twelve hours and largely disappearing after twenty-four hours. With repeated injections, these changes tend to persist.

Presumably a similar mechanism accounts for the lymphopenia that has been observed to occur in man in the period of three to twenty-four hours after intravenous administration of various bacterial proteins.[23]

Dole, Watson and Rothbard[24] observed that in beta hemolytic streptoccal infections, there was a general correlation between the increase in gamma globulins as measured electrophoretically with the titer of antistreptolysin although the increase in antistreptolysin titer *per se* would not seem to be sufficient to account for the marked elevation of the serum gamma globulin that was observed frequently in these patients.

There is no conclusive evidence at the present time that all serum gamma globulin is derived from lymphocytes. Moreover, it is possible that protein depletion or other factors still unknown may impair antibody production without implying any defect in the lymphocyte mechanism in ininstances where antibody production is impaired.[19,25,26]

As has been indicated, a decrease in total lymphocytes and a rise in "gamma globulin" was observed in the control subjects following administration of typhoid vaccine. This effect was greatest at the end of eighteen hours and rapidly disappeared thereafter. It is possible that even greater changes in these constituents might have occurred if similar studies had been made earlier than eighteen hours after injection of the vaccine. Without any significant change in the total lymphocytes per c. mm. a second rise in "gamma globulin" was observed on the ninth day and largely disappeared by the eleventh day after administration of vaccine. (Fig. 4.) This secondary increase in "gamma globulin" coincides with the time of development of maximal circulating antibody titer to the typhi H antigen.This does not imply that the rise in "gamma globulin" on the ninth day was attributable wholly to an increase in antibodies to the typhi vaccine. This is even more apparent when it is noted that while the "gamma globulin" returns to normal rapidly, the decrease in circulating antibodies to the typhi H antigen is slow, the high titers often persisting for many weeks.

In the patients receiving massive doses of salicylates the observed changes occurring after administration of typhoid vaccine differed strikingly from those noted in the controls. Local reactions were milder in the patients receiving salicylates. No systemic reaction occurred in any patient receiving salicylate medication after administration of the vaccine. This appears significant inasmuch as seven of nine control subjects who had been immunized previously developed systemic reactions after readministration of vaccine while none of nine subjects receiving salicylates in whom immunization had been instituted previously developed any systemic reaction. There was no significant rise in the plasma fibrinogen, the total leukocyte count or the total number of granulocytes in the patients receiving salicylate medication. Likewise, no significant increase in plasma fibrinogen or erythrocyte sedimentation rate, and no immediate or delayed rise in "gamma globulin" occurred in this group. It did appear that some reduction in total lymphocytes per c. mm. followed the injection of the vaccine in the patients receiving salicylate medication. Antibody production appeared to be impaired significantly in the patients receiving salicylates as opposed to the controls.

Swift injected various antigens into rabbits receiving large doses of salicylates and observed that circulating antibody production was impaired but not blocked completely in these animals.[27] Homburger[28] observed marked reduction of circulating antibody titer after administration of large doses of salicylates to rabbits and guinea pigs that were receiving injections of rhesus cells. In man, however, the evidence that salicylate medication impairs antibody production is equivocal. Perry[29] found no impairment of antibody response following administration of typhoid vaccine to patients who were receiving 2 to 3 Gm. of acetylsalicylic acid daily. Coburn and Moore[30] administered salicylate therapy prophylactically to groups of rheumatic subjects at a time when they developed beta hemolytic streptococcal pharyngitis. The dosage was 4 to 6 Gm. a day. The antistreptolysin response in the group receiving salicylates was similar to that in a control group. Rantz, Boisvert and Spink[31] treated a group of patients with hemolytic streptococcal pharyngitis with 10 Gm. of sodium salicylate daily for one week. This did not diminish the percentage of individuals exhibiting an antibody response and did not reduce the mean increase in antistreptolysin. With the exception of the latter study, the doses of salicylates employed may be considered as inadequate to produce significant plasma salicylate levels. In no instance was mention made of determinations of the plasma salicylate level. Our own studies appear to indicate that typhoid vaccine administered to patients in whom high plasma salicylate levels (300 to 400 micrograms per cc.) are maintained, evokes less circulating antibody production than occurs in control subjects. We did observe that circulating antibodies to the typhoid H antigen may persist during prolonged courses of salicylate medication in patients who have residual antibodies from previous typhoid vaccine administration. Here, however, renewed administration of antigen did not result in as great an increase in antibody titer as might be expected from the response of the antibody titer in previously immunized control subjects to whom this vaccine was readministered. The argument that the patients receiving salicylate medication might not be able to develop high antibody titers because of their disease (rheumatic fever, rheumatoid arthritis, etc.) does not seem valid inasmuch as two subjects with acute rheumatic fever not treated with salicylate developed antibody titers as high as healthy control subjects after injection of typhoid antigen.

It is difficult to ascribe the differences in response to typhoid vaccine between the control group and the group receiving salicylate medication to any single mechanism. A number of possibilities present themselves.

The apparent failure to observe the changes in the salicylate group as opposed to the control group might be explained by assuming that the salicylate medication in some way modified the bacterial proteins so as to render them less toxic and less antigenic. Swift[27] reported that incubation of typhoid organisms with salicylates prior to administration into rabbits receiving salicylate medication resulted in less antibody formation than was observed in rabbits which were immunized with untreated antigen while receiving salicylates. He does not define clearly the concentration of salicylate which was employed in treating the typhoid organism but his statements suggest that it was a far higher concentration than could be obtained *in vivo*.

A further possibility is that the injected organisms and their toxins are removed more rapidly from the circulation than in the controls. Beeson[32] observed that after repeated administration of typhoid organisms to rabbits, their febrile response became less with succeeding injections and was restored to its former magnitude when the reticulo-endothelial system was blocked by injections of thorotrast. This seemed to indicate that the reticulo-endothelial system removed the organisms more rapidly from the circulation in these hyperimmunized animals. At present we have no information as to whether or not salicylate medication stimulates the reticulo-endothelial system.

The failure to observe a rise in serum "gamma globulin" and the impaired antibody response in the patients receiving salicylate medication suggests impaired production of antibody by the lymphocytes either directly or indirectly through the pituitary-adrenal cortical stimulation. As additional evidence it may be pointed out that we have observed in both normal subjects and in patients with acute rheumatic fever or rheumatoid arthritis that prolonged administration of large doses of salicylates with maintenance of plasma salicylate levels above 300 micrograms per cc., produces a definite decrease in the serum "gamma globulin" as determined chemically.[33] This finding should be confirmed with electrophoretic studies in order to preclude certain difficulties which might arise from qualitative changes in the proteins in patients receiving salicylate medication.

Finally, there is a certain amount of evidence which indicates that salicylate medication results in selective liver damage. It is conceivable that with impaired liver function, the necessary precursors for antibody production may be lacking. The most striking evidence of impaired liver function in patients receiving salicylates is the hypoprothrombinemia which may occur. Elsewhere we have considered this problem and have presented other evidence for selective liver damage in patients receiving salicylate medication.[34,35] Recently, Rapoport and Guest[36] reported that the decrease in plasma fibrinogen which frequently is observed in patients receiving salicylate medication is additional evidence of selective liver damage since this decrease in plasma fibrinogen also was noted in patients with diseases other than rheumatic fever while massive doses of salicylates were being administered. Our finding that the plasma fibrinogen does not rise after administration of typhoid vaccine would be in accord with this view. However, it is equally possible in our cases that the milder local reactions observed to occur in patients receiving salicylate medication after injection of typhoid vaccine might have afforded less stimulus for an increase in plasma fibrinogen.

CONCLUSIONS

Typhoid vaccine was administered intramuscularly to eighteen control subjects and to fourteen patients who were receiving massive salicylate therapy.

Antibody formation to the typhoid H and O antigens was suppressed in the patients receiving salicylate medication as opposed to the control subjects.

Individuals receiving typhoid vaccine intramuscularly usually develop a transient leukocytosis with an increase in granulocytes and a lymphopenia. In addition, a rise in the plasma fibrinogen and in the erythrocyte sedimentation rate occurs after injection of vaccine. As determined chemically, the "gamma globulin" fraction of serum increases immediately following vaccine administration, returns rapidly to its original level and then rises again during the second week following vaccine administration. This secondary rise coincides with the development of the maximum antibody titer to the typhi H antigen.

In patients receiving salicylate medication, these changes do not occur or are slight in character following injection of vaccine.

In patients previously immunized with typhoid vaccine, readministration frequently results in systemic reactions. No systemic reactions occurred, however, in previously immunized patients receiving salicylate medication when the vaccine was reinjected.

Possible means whereby salicylate medication alters the response to typhoid vaccine are considered.

Dr. M. M. Wintrobe and Dr. George Sayers gave aid in the criticism of this manuscript.

REFERENCES

1. Brodie, B. B., Udenfriend, S. and Coburn, A. F. The determination of salicylic acid in the plasma. *J. Pharmacol. & Exper. Therap.*, 80: 114, 1944.
2. Kingsley, G. R. The determination of serum total protein, albumin and globulin by the biuret method. *J. Biol. Chem.*, 131: 197, 1939.
3. Cullen, G. E. and Van Slyke, D. D. Determination of the fibrin, globulin and albumin nitrogen of blood plasma. *J. Biol. Chem.*, 41: 587, 1920.
4. Howe, P. E. The determination of proteins in blood—a micro method. *J. Biol. Chem.*, 49: 109, 1921.
5. Gutman, A. B., Moore, D. H., Gutman, E. B., McClellan, V. and Kabat, E. A. Fractionation of serum proteins in hyperproteinemia, with special reference to multiple myeloma. *J. Clin. Investigation*, 20: 765, 1941.
6. Jager, B. V. and Greenberg, G. R. Preliminary studies of gamma globulins as determined by chemical methods. *Rocky Mountain M. J.*, 43: 473, 1946.
7. Jager, B. V. Unpublished data.
8. Enders, J. F. Chemical, clinical and immunological studies of the products of human plasma fractionation. x. The concentrations of certain antibodies in globulin fractions derived from human blood plasma. *J. Clin. Investigation*, 23: 510, 1945.
9. Wintrobe, M. M. and Landsberg, J. W. A standardized technique for the blood sedimentation test. *Am. J. M. Sc.*, 189: 102, 1935.
10. Tillett, W. S. The fibrinolytic activity of hemolytic streptococci. *Bact. Rev.*, 2: 161, 1938.
11. Ham, T. H. and Curtis, F. C. Sedimentation rate of erythrocytes. Influence of technical erythrocyte and plasma factors and quantitative comparison of five commonly used sedimentation methods. *Medicine*, 17: 447, 1938.
12. Fahraeus, R. The suspension stability of the blood. *Physiol. Rev.*, 9: 241, 1929.
13. Gilligan, D. R. and Ernstene, A. C. The relationship between the erythrocyte sedimentation rate and the fibrinogen content of plasma. *Am. J. M. Sc.*, 187: 552, 1934.
14. Oakley, W. Erythrocyte sedimentation and the plasma fibrinogen. *Lancet*, 1: 312, 1938.
15. Favorite, G. O. and Morgan, H. R. Therapeutic induction of fever and leucocytosis using a purified typhoid pyrogen. *J. Lab. & Clin. Med.*, 31: 672, 1946.
16. Ehrich, W. E. and Harris, T. N. The formation of antibodies in the popliteal lymph node in rabbits. *J. Exper. Med.*, 76: 335, 1942.
17. Dougherty, T. F., Chase, J. H. and White, A. The demonstration of antibodies in lymphocytes. *Proc. Soc. Exper. Biol. & Med.*, 57: 295, 1944.
18. Ehrich, W. E. and Harris, T. N. Observations on the function of the lymphocytes. *Am. J. M. Sc.*, 101: 129, 1945.
19. White, A. and Dougherty, T. F. The pituitary adrenotropic hormone control of the rate of release of serum globulins from lymphoid tissue. *Endocrinology*, 36: 207, 1945.
20. Kass, E. H. Occurrence of normal serum gammaglobulin in human lymphocytes. *Science*, 101: 337, 1945.
21. White, A. and Dougherty, T. F. Influence of pituitary adrenotrophic hormone on lymphoid tissue structure in relation to serum proteins. *Proc. Soc. Exper. Biol. & Med.*, 56: 26, 1944.
22. Dougherty, T. F., Chase, J. H. and White, A. Pituitary-adrenal cortical control of antibody release from lymphocytes. An explanation of the

anamnestic response. *Proc. Soc. Exper. Biol. & Med.*, 58: 135, 1945.
23. SUNDELIN, F. Lymphocytopenia and fever. *Acta med. Scandinav.*, 99: 563, 1939.
24. DOLE, V. P., WATSON, R. F. and ROTHBARD, S. Electrophoretic changes in the serum protein patterns of patients with scarlet fever and rheumatic fever. *J. Clin. Investigation*, 24: 648, 1945.
25. CANNON, P. R. Antibody production and the anamnestic reaction. *J. Lab. & Clin. Med.*, 28: 127, 1942.
26. CANNON, P. R. Antibodies and the protein-reserves, *J. Immunol.*, 44: 107, 1942.
27. SWIFT, H. The action of sodium salicylate upon the formation of immune bodies. *J. Exper. Med.*, 36: 735, 1922.
28. HOMBURGER, F. Sodium salicylate inhibiting anti-Rh immunization in animals. *Proc. Soc. Exper. Biol. & Med.*, 61: 101, 1946.
29. PERRY, C. B. The action of salicylates on the development of antibodies following anti-typhoid inoculation. *J. Path. & Bact.*, 53: 291, 1941.
30. COBURN, A. F. and MOORE, L. V. Salicylate prophylaxis in rheumatic fever. *J. Pediat.*, 21: 180, 1942.
31. RANTZ, L. A., BOISVERT, P. J. and SPINK, W. W. Hemolytic streptococcal sore throat: Antibody response following treatment with penicillin, sulfadiazine and salicylates. *Science*, 103: 352, 1946
32. BEESON, P. B. Development of tolerance to typhoid bacterial pyrogen and its abolition by reticuloendothelial blockade. *Proc. Soc. Exper. Biol. & Med.*, 61: 248, 1946.
33. JAGER, B. V. Unpublished data.
34. CLAUSEN, F. W. and JAGER, B. V. The relation of the plasma salicylate level to the degree of hypoprothrombinemia. *J. Lab. & Clin. Med.*, 31: 428, 1946.
35. JAGER, B. V. and ALWAY, R. The treatment of acute rheumatic fever with large doses of sodium salicylate. *Am. J. M. Sc.*, 211: 273, 1946.
36. RAPOPORT, S. and GUEST, G. M. Effect of salicylate on plasma fibrinogen and sedimentation rate in rheumatic and non-rheumatic patients. *Proc. Soc. Exper. Biol. & Med.*, 61: 43, 1946.

Gastroscopy with Transparent Balloon*

Method for the Visualization of the "Blind Areas"

HENRY COLCHER, M.D.
NEW YORK, NEW YORK

WITH the flexible gastroscope (Wolf-Schindler) about four-fifths of the stomach can be visualized. There are, however, a number of important areas that cannot be seen. These are the so-called "blind areas"[1,2] or "zones interdites."[3] The extent of these areas varies somewhat with the shape of the stomach and the conditions under which the examination is performed. Figure 1 is a schematic drawing of the stomach in the left lateral position with the usual blind areas labelled alphabetically. A description of the drawing follows:

A represents the lesser curvature of the antrum. This area is often difficult to visualize because of the angulation of the stomach. The examination of the antrum is important since a great number of malignant lesions are situated in that region; B represents a small part of the greater curvature forming the lower pole of the stomach and a strip of the posterior wall on which the gastroscope lies. This zone is often the site of the stoma of posterior gastroenterostomy where marginal ulcers may arise;[4] C illustrates a region high up in the fundus which is hidden from view. Unfortunately, this is an area which is also difficult to examine roentgenologically because manual compression of this portion is unsatisfactory; D represents a small zone on the posterior wall near the cardia and 1 to 2 cm. of the lesser curvature immediately below the cardia where the objective is too close to the mucosa. The mucosa may be lifted somewhat by the device suggested by Rogers.[5] This method may also be used for the examination of the posterior wall and greater curvature. (Fig. 1, zone B.)

Of these four zones the "blind area" of the antrum is the most important as radiologists are often unable to make a definite

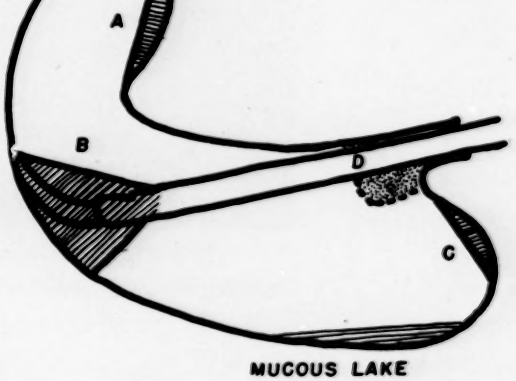


FIG. 1. "Blind areas" of the stomach. The shaded areas, A, B, C and D, are seldom visualized during gastroscopic examination.

diagnosis of the nature of craters seen in this region. Gastroscopic examination of this area during various phases of respiration with observation of the peristaltic movements may enable one to study the antrum to greater advantage.[1,2,6,7] In the majority of instances, however, it is still impossible to visualize the lesser curvature satisfactorily. Berry[8] suggests that gastroscopy be performed with the patient in the right lateral position, since he observed in twenty-four examinations that "the visualization of the blind area of the antrum was improved in

* From the Research Service, First (Columbia) Division, Goldwater Memorial Hospital, Department of Hospitals and the Department of Medicine, Columbia University, College of Physicians and Surgeons, New York, N. Y.

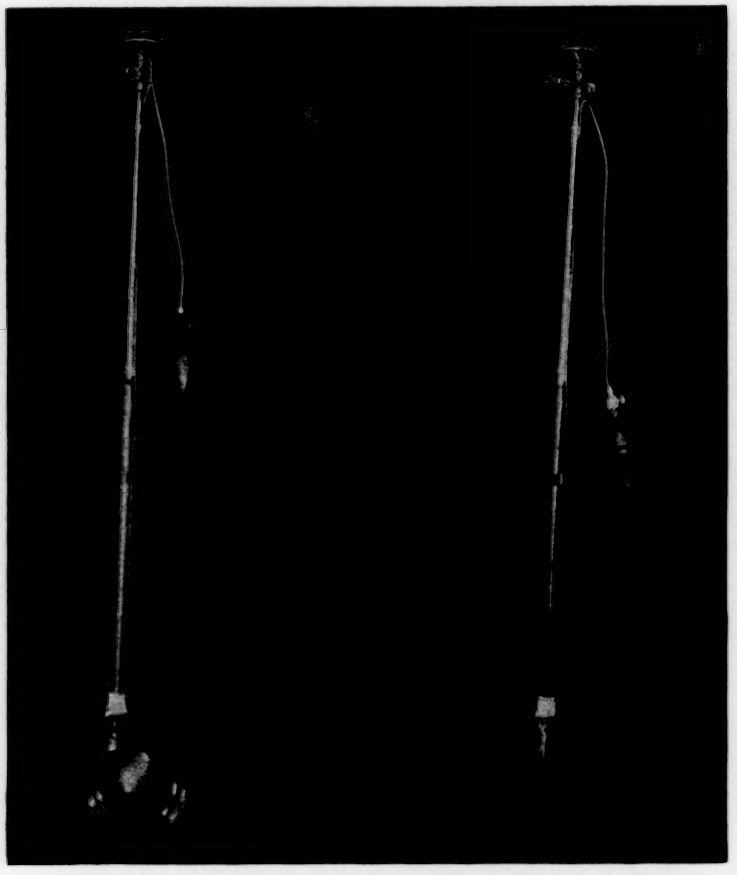


FIG. 2. Wolf-Schindler gastroscope with attachments: balloon, catheter and insufflation bulb. Lower balloon contains approximately 400 ml. of air.

two-thirds of the cases." The right lateral position has disadvantages and the majority of gastroscopists prefer the left lateral position. In the present paper a modification of the gastroscopic technic is presented in an attempt to obtain better visualization of the lesser curvature of the antrum. The stomach is distended by inflating a rubber balloon attached to the lower end of the gastroscope. In this way the lesser curvature is straightened.

METHOD AND RESULTS

During the usual gastroscopic procedure air is injected through several small openings, situated immediately above the objective, to separate the gastric walls. Small amounts of air are used to avoid discomfort, regurgitation through the cardia and interference with peristalsis.

The following modification of the gastroscopic technic is suggested in order to obtain a more uniform distention of the stomach. A transparent rubber balloon is adapted to the tip of the gastroscope. The balloon covers the rubber finger, the electric bulb and the objective and is attached immediately above the latter. A non-collapsible tube is necessary for the insufflation and withdrawal of air. A ureteral catheter (Eynard No. 8) with a rubber extension is attached to the shaft of the instrument. The gastroscope is introduced in the usual manner and 50 ml. of air injected into the balloon. (Fig. 2.) After the usual gastroscopic examination more air is introduced into the

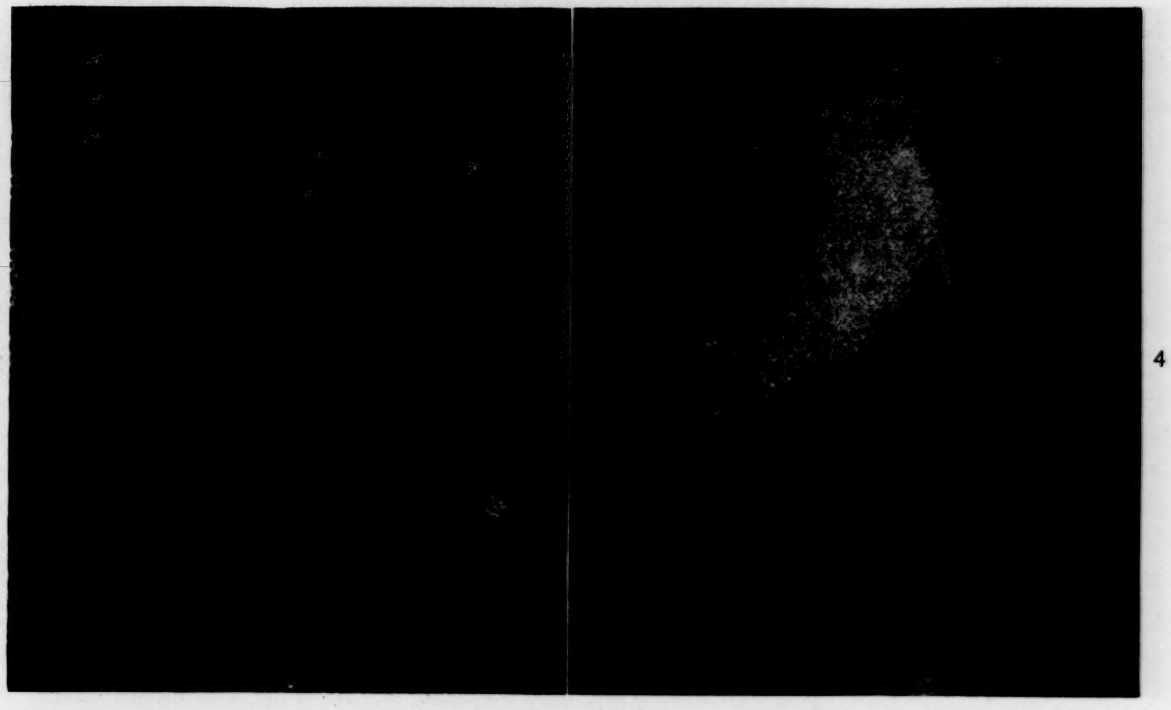


FIG. 3. Anteroposterior view of a stomach containing a balloon distended with about 800 ml. of air. Note the position of the angulus (*a*) and the duodenal bulb (*b*).
FIG. 4. Stomach distended with about 900 ml. of air; the lesser curvature is straight.

balloon. The stomach is sufficiently distended with about 500 to 800 ml. of air and becomes somewhat oval or spherical. The position of the pylorus varies with the amount of air and the degree of distention. By slowly withdrawing and rotating the gastroscope one can readily examine the antrum and then proceed upward to the corpus and fundus. The rugae are obliterated by this degree of distention but reappear when the balloon is partially deflated.

Figure 3 is a radiographic film taken in the anteroposterior position and shows the shape of the stomach containing a balloon inflated with approximately 800 ml. of air. The position of the angulus can be noted. There is a small amount of air in the duodenal cap.

Figure 4 represents a film taken with a larger balloon and a stomach tube kept semirigid by a wire in order to simulate a gastroscope. The stomach was distended with about 900 ml. of air. The angulus is lifted by the balloon.

Although our experience with this method is still limited, the following points have been noted. The attachment of the balloon-catheter unit to the gastroscope does not add to the difficulty of introduction of the gastroscope. The lumen of the catheter being small, it is necessary to allow about one minute for the balloon to empty before withdrawing the instrument. The volume of air necessary to lift the angulus is approximately one-third to one-half the capacity of the average stomach and does not seem to add to the discomfort of the patient. The gastroscope can be moved around with ease in the inflated stomach. The bulb and the objective are always protected by the rubber balloon; there is less danger of causing a gastric burn by a hot bulb. This method avoids the changing of views caused by peristalsis and escape of air through the pylorus or cardia.

The color of the mucosa and the character of the rugae can be studied, either at the beginning or at the end of the examination, using very little air.

This method has been tested in thirteen patients. In all but one, the pylorus and the entire circumference of the antrum corpus were visualized, including the so-called blind areas A and B. (Fig. 1.) In one patient the pylorus was not seen and the angulus could not be lifted with the balloon containing about 800 ml. of air. This patient had a cholecystectomy for cholelithiasis and cholecystitis two years ago and at present has chronic myelogenous leukemia with hepatomegaly. These factors may have contributed to the failure of visualization of the pylorus. *

SUMMARY

The use of a transparent balloon attached to the lower end of a gastroscope is suggested for distention of the stomach. When inflated it straightens the lesser curvature and thus makes possible a more complete gastroscopic examination.

* Since submission of the manuscript fourteen additional patients were examined with this technic. The lesser curvature of the antrum and the pylorus were visualized in all fourteen cases.

The hitherto blind areas on the lesser curvature of the antrum and the posterior wall of the corpus were visualized in twelve of thirteen patients.

The author is indebted to Dr. Henry K. Taylor, Director of the Department of Radiology, Goldwater Memorial Hospital, for his invaluable help and guidance. He also wishes to express his thanks to Dr. Frank B. Berry, Director of the First Surgical Division, Bellevue Hospital, for the privilege of examining six patients from his Service and Dr. Robert H. Wylie for his generous cooperation.

REFERENCES

1. Schindler, R. Gastroscopy. The Endoscopic Study of Gastric Pathology. Chicago, 1937. The University of Chicago Press.
2. Henning, N. Textbook of Gastroscopy. Translated by H. W. Rodgers, Oxford, England. London, 1937. University Press.
3. Moutier, F. Traité de Gastroscopie. Paris, 1935. Masson et Co.
4. Jankelson, I. R. and McClure, C. W. Limitations of gastroscopy. *New England J. Med.*, 224: 64, 1940.
5. Rodgers, H. W. Device for increasing field in gastroscopy. *Lancet*, 2: 438, 1936.
6. Benedict, E. B. Gastroscopy. Oxford Medicine. Vol. 111, 122 (17). New York, 1941. Oxford University Press.
7. Massion, J. and Colcher, H. Note sur la gastroscopie de l'ulcere juxta-pylorique. *J. belge de gastroenterologie*, 8: 174, 1940.
8. Berry, L. H. Right side gastroscopic technique. *Rev. Gastroenterol.*, 8: 267, 1941.

Chemical Evaluation and Labeling of Protein Hydrolysates for Human Consumption*

F. HOMBURGER, M.D. *and* N. F. YOUNG, PH.D.
NEW YORK, NEW YORK

THE extensive use of protein hydrolysates in medicine and surgery and the fact that large quantities of these preparations are often administered creates a distinct need for exact knowledge of their composition.[1] The information given at present on the labels of many protein hydrolysates is insufficient. It is the purpose of this paper to call attention to this fact and to suggest measures designed to ameliorate the present situation.

METHODS

The following studies were undertaken on samples of ten different brands of protein hydrolysates. Total nitrogen was estimated by the standard micro-Kjeldahl method, ammonia by aeration according to Van Slyke[2] and creatine by Folin's autoclave method.[3] Total amino nitrogen was determined by five methods: (1) Nitrous acid method of Van Slyke;[4] (2) Albanese's copper complex method;[5] (3) formol titration (F_s) under conditions dictated by general considerations;[6] (4) formol titration (F_w) according to specific conditions given by Winton[7] and (5) free amino nitrogen by the ninhydrin method of MacFayden and Van Slyke.[8] Sodium and potassium were estimated by flame photometry.[9] Total phosphorus was determined by the method of Fiske and Subbarow.[10]

RESULTS

The compositions of the hydrolysates studied are given in Table I. It will be seen that fairly large discrepancies occur in amino nitrogen content as determined by different methods. In most cases the method used in determining the amino nitrogen content given on the label of the product is not specified. The figures in column F_s represent, with one exception, the highest amino nitrogen values for a given product. Except for hydrolysates 3, 4 and 5, on which the label values for amino nitrogen are specified as having been obtained by the nitrous acid method, the crude formol figures (F_s) correspond most closely to label figures. Because of the danger of falsely high values due to interference by phosphates or constituents containing no amino nitrogen, the more refined formol titration figures (F_w) more nearly represent amino nitrogen.

One product, No. 10, which is sold and advertised as a protein hydrolysate, actually contains only 7 per cent of the nitrogen in the form of amino nitrogen, of this 2.3 per cent is in the form of free amino acids.

The ammonia and creatine values are reasonably uniform and low, the latter being somewhat high in those hydrolysates produced from animal sources.

The sodium content of the hydrolysates varied over a wide range. In at least one product (No. 6), sodium chloride has been added, presumably to improve flavor. The potassium and phosphorus contents were excessive in no samples and were frequently very low. The contents probably reflect those of the protein sources. The content

* From the Laboratory of Clinical Investigation, Sloan-Kettering Institute for Cancer Research, New York, N. Y. This work was aided by grants from the National Cancer Institute and the Teagle Fellowship Foundation.

of these minerals should be increased if the products are to be used as the sole source of protein.

COMMENTS AND SUMMARY

A study of the chemical composition of ten commercially available protein hydrolysates revealed that they vary widely in composition and that such variation is not always indicated by the labels. The application of a uniform method for the determination of the amino nitrogen content is recommended so that a direct comparison among the various products is possible. Since the only reason for producing a hydrolysate is to degrade the protein to more readily available constituents with a higher amino nitrogen content, the physician should be able to compare the commercial preparations in this respect.

The formol titration method was found to be unreliable for the determination of the amino nitrogen content because it seemed to be influenced by the phosphate content as well as by other factors. The best method for the amino nitrogen determination would at present appear to be the nitrous acid method. This method, used with proper precautions, has been found reliable for many years in a variety of materials. Newer methods, such as that developed by Albanese, should be given more extensive trial before adoption as a procedure for establishing important food standards. Of the numerous colorimetric procedures, none is suitable since their application to a crude mixture yields unreliable results. The ninhydrin method determines the free amino acids present rather than the amino nitrogen content.

As a further safeguard against the use of ineffective medication, the biologic value of these preparations in man should be tested and expressed in standardized form. The wide variation of sodium chloride content in the hydrolysates studied indicates the desirability of a statement on the label of exactly how much salt any given product contains. If sufficient amounts of these products are given to supply 0.6 Gm. of nitrogen/day/Kg. during the postoperative phase, as has been recommended, excessive amounts of sodium chloride would be administered in some instances.

The content of other minerals, such as potassium, in these products should also

TABLE I

CHEMICAL COMPOSITION OF TEN PROTEIN HYDROLYSATES AS INDICATED ON THE LABELS AND AS DETERMINED. ALL FIGURES ARE IN GM. PER CENT

No.	Source	Total Nitrogen		Creatine plus Creatinine	Ammonia	Amino Nitrogen†						Amino N	Mineral Composition			Additions
		Determined	Label*			Cu	NO_2	F_W	F_S	Ninhydrin	Label*	Total N	Na as NaCl	K	P	
1	Casein.....	12.0	12.0	0.06	0.46	6.4	6.0	6.5	7.3	5.7	7.5	0.50	0.5	Tr	0.5	0
2	Beef blood....	11.0	11.0	0.07	0.24	6.3	5.1	5.7	5.8	4.4	6.0	0.46	0.6	0.1	0.4	0
3	Casein.....	12.8	13.0	0.04	0.27	4.4	3.1	3.5	3.5	1.6	3.0	0.24	3.1	Tr	0.84	0
4	Casein.....	12.9	13.0	0.02	0.12	3.4	3.1	3.0	3.6	2.3	3.0	0.24	5.3	Tr	0.85	0
5	Casein.....	12.9	13.0	0.03	0.11	4.4	3.1	3.1	3.4	1.7	3.0	0.24	2.9	Tr	0.84	0
6	Casein.....	8.9	....	0.16	0.16	3.8	3.2	...	3.2	2.3	...	0.36	21.0	0.6	0.9	Vitamins, iron, Ca, P
7	Lactalbumin...	11.3	11.5	0.1	0.25	6.6	6.4	6.6	7.4	5.4	7.5	0.57	0.3	0.1	0.14	0
8	Brewers' yeast..	11.5	11.5	0.2	0.12	2.6	4.0	4.3	5.9	...	6.0	0.35	4.5	2.3	2.2	B vitamins (natural)
9	Yeast, meat...	6.6	6.8	0.15	0.21	2.9	2.8	3.0	3.2	2.5	3.6	0.44	0.4	2.4	1.3	Vitamins, carbohydrate
10	Beef, milk, wheat, yeast.	7.5	7.2	0.32	0.10	0.5	0.5	0.7	0.8	0.3	...	0.07	4.8	1.7	0.74	Carbohydrates

* As labelled by manufacturer.

† As determined by the copper complex method (Cu), the nitrous acid method (NO_2), formol titration according to Winton (F_W), formol titration by usual technic (F_S) and by the ninhydrin method.

be indicated so that when they are used as the chief or exclusive source of nutriment the risk of depleting the patient of these minerals can be avoided.

REFERENCES

1. Homburger, F. Use of protein hydrolysates by mouth. *Am. J. Med.*, 3: 430, 1947.
2. Peters, J. and Van Slyke, D. D. Urease Method with Aeration and Titration for both Urea and Ammonia. Quantitative Clinical Chemistry. Vol. 2, p. 549. Baltimore, 1931. Williams and Wilkins.
3. Folin, O. On the determination of creatine, creatinine in urine. *J. Biol. Chem.*, 17: 469, 1914.
4. Van Slyke, D. D. A newer method for quantitative determination of aliphatic amino groups, I and II. *J. Biol. Chem.*, 9: 185–204, 1912 and 12: 275–284, 1913.
5. Albanese, A. and Irby, V. Determination of urinary amino nitrogen by copper method. *J. Biol. Chem.*, 153: 583, 1944.
6. Levy, M. Equilibria in the formol titration. *J. Biol. Chem.*, 99: 767–779, 1932.
7. Winton and Winton. Analysis of Foods. Pp. 77–78. London, 1945. John Wiley and Sons.
8. Van Slyke, D. D., MacFayden, D. A. and Hamilton, P. B. Gasometric determination of amino acids in urine by ninhydrin-carbon dioxide method. *J. Biol. Chem.*, 150: 251–258, 1943.
9. Barnes, R. B., Richardson, D., Berry, V. W. and Hood, R. L. Flame photometry. *Ind. Eng. Chem. Anal. Ed.*, 17: 605, 1945.
10. Fiske, C. H. and Subbarow, Y. The colorimetric determination of phosphorus. *J. Biol. Chem.*, 66: 375, 1925.

Use of Protein Hydrolysates by Mouth*

F. HOMBURGER, M.D.
NEW YORK, NEW YORK

THERE is at present much confusion regarding the indications for the use of protein hydrolysates as well as in the choice of the hydrolysate best suited for each clinical problem. It is not always easy from a perusal of the advertising literature to decide whether a product is a protein hydrolysate, an amino acid mixture or a protein concentrate. It is the purpose of this paper to clarify the situation regarding the administration of protein derivatives by way of the gastrointestinal tract.

Protein hydrolysates are obtained by the digestion of various proteins by chemical or enzymatic methods, i.e., by acid or alkaline hydrolysis or by the use of pancreatic or other proteolytic enzymes. In this manner the protein is broken down into amino acids of which the major part remain linked to each other in the form of di- or polypeptides, while a small fraction is present in the free state. A protein hydrolysate is thus clearly different from native protein, from protein concentrates and from mixtures of pure amino acids.

The preparation of amino acid mixtures and of protein hydrolysates represents a great advance in medical and surgical therapeutics, because such products have made possible intravenous feeding of the "building stones" of protoplasm in cases when parenteral nutrition is necessary; such treatment previously had been limited to carbohydrates, salt and fluids. The use of amino acid mixtures and protein hydrolysates *by vein* has been extensively studied and described in the literature and will not be dealt with in this communication.[1] There are definite indications for *enteral* administration of these products; but their scope of useful application, while important, is more narrow than that claimed in some commercial advertising.

INDICATIONS FOR PROTEIN HYDROLYSATES

In some patients the protein of the diet should be supplemented. In these instances it is usually preferable to use protein concentrates rather than hydrolysates. In the presence of intact digestive mechanisms there is no reason to prefer hydrolyzed to native protein,[2,3] except perhaps for smaller bulk. Furthermore, animal experiments seem to indicate that full proteins by mouth are twice to three times more effective than protein hydrolysates by vein.[4]

In a few instances protein hydrolysates provide the only means for the administration of proteins. Among these are cases of resection of the head of the pancreas for carcinoma of that organ, sometimes associated with inability to digest proteins, and cases of impaired protein digestion in chronic pancreatitis. Patients with ulcerative colitis sometimes benefit from protein hydrolysates and in some cases of mechanical rearrangement of the intestine with short circuits following surgery they may be the only means of protein nutrition. There are other specific indications, such as the use of protein hydrolysates for the treatment of gastric ulcer and pylorospasm,[5] which will

* From the Laboratory of Clinical Investigation, Sloan-Kettering Institute for Cancer Research, New York, N. Y. This study was aided by grants from the National Cancer Institute and the Teagle Fellowship Fund for Cancer Research.

not be discussed here. In addition, one encounters situations when large amounts of protein can best be administered in the hydrolyzed form. This is the case whenever large losses of nitrogen occur at a time when the patient is unable to eat native protein, as during periods of serious infection or following operation, especially surgery of the gastrointestinal tract.

SPECIAL CONSIDERATIONS

The following special considerations will deal primarily with the use of protein hydrolysates in the postoperative phase.

The aim of protein therapy in general is the administration of sufficient protein (nitrogen) to obtain positive nitrogen balance. The nitrogen utilized serves to replenish deficient stores of tissue and circulating plasma proteins. It is apparently possible in certain instances to achieve positive nitrogen balance over a long period of time in hypoproteinemic patients without obtaining any increase in the amount of plasma protein.[6] This emphasizes the necessity of following plasma protein regeneration directly, by measuring the circulating plasma protein levels instead of relying on the administration of "adequate amounts" of protein. Infusion of plasma may be necessary in addition to high protein feeding in order to restore plasma proteins to normal. The amounts of protein needed to replenish protein stores may be truly tremendous. Thus to insure optimal protein repletion in the postoperative phase as much as 0.6 Gm of nitrogen (3.75 Gm. of protein) per Kg. of body weight per day may be necessary.[7] This is of the order of 200 to 250 Gm. of protein per day in patients of average weight.

When, based upon the preceding considerations, such large amounts of protein hydrolysate are being given, the practitioner must be certain that the product used will give the best possible results and will not be toxic in such large amounts. In this connection it should be recalled that occasionally some hydrolysates may cause histamine-like reactions when given in large amounts. In at least one instance the administration of a hydrolysate (not now on the market) produced renal colic with the appearance of large amounts of urinary sediment, the nature of which was not ascertained.[8]

To assure optimal results some properties of the hydrolysates have to be considered and a certain basic knowledge of nutritional physiology has to be applied.

For instance, great losses of nitrogen will occur if large amounts of protein are being given unaccompanied by adequate amounts of energy sources such as carbohydrate and fat. In order to assure positive nitrogen balance these "protein sparers" have to be added. Such large amounts of carbohydrate in turn increase the demand for vitamins, especially those of the B complex, because of the catalytic rôle of these vitamins in carbohydrate metabolism and in the utilization of amino acids. A safe and reasonable daily vitamin supplement is the following:[9]

Vitamin C	500 to 1,000 mg.
Thiamine	20 to 40 mg.
Riboflavin	20 to 40 mg.
Niacin	150 to 300 mg.
Vitamin A	15,000 U.S.P. units
Vitamin D	1,500 U.S.P. units

The vitamin supplement can be given with the hydrolysate by tube or by mouth, unless there is known impairment of absorption from the gastrointestinal tract, in which case it must be given parenterally.

The amounts of minerals provided (usually well covered in normal diets of average composition) should be carefully considered when the entire protein intake, or most of it, is derived from hydrolysates, and even more so when energy is supplied as pure sugar and vitamins in their synthetic form. Normal average daily intakes of the various minerals are about as follows:[10]

Potassium	3.39	Gm.
Calcium	0.73	Gm.
Sodium	1.94	Gm.
Magnesium	0.34	Gm.
Phosphorus	1.58	Gm.
Sulfur	1.28	Gm.
Iron	0.0307	mg.

Adequate amounts of minerals are necessary when the replacement of lost protein stores is intended, not only because of daily maintenance requirements but also to provide the building stones for the new protoplasm the organism is expected to build from the protein offered. Since potassium, phosphorus and sulfur enter the structure of protoplasm it is essential that all of these components be provided in addition to the amino acids and polypeptides. It is particularly necessary to supply potassium for intracellular fluid and sodium for extracellular fluid since there is no reserve store of these elements comparable to the stores of calcium, phosphorus and magnesium in bone. How widely the composition of different hydrolysates may vary with regard to nitrogen content and minerals is shown in Figure 1.

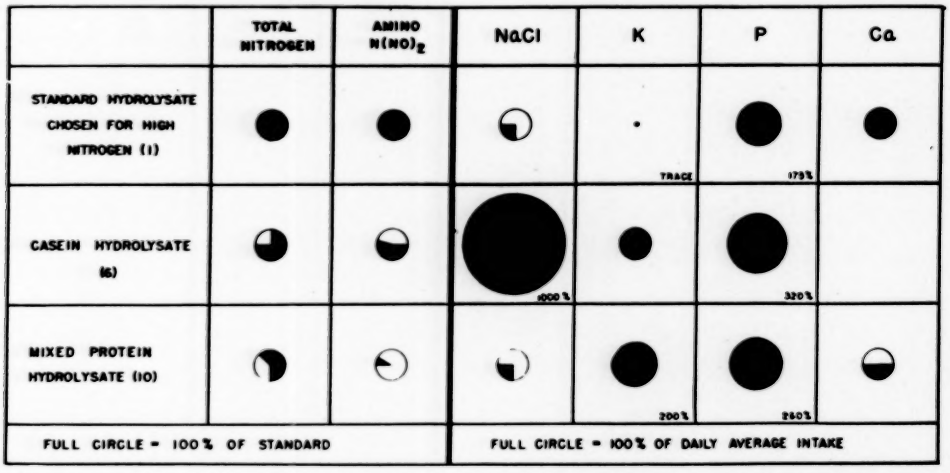


FIG. 1. Chemical composition of 350 Gm. of three different protein hydrolysates.

The actual amount of protein required by each individual patient can be determined accurately only by balance studies and measurements of plasma protein regeneration; it varies considerably. The optimal daily requirement of normal individuals seems to be approximately 1 Gm. of protein per Kg. of body weight, whereas the requirement in the postoperative phase is considerably larger, about 0.6 Gm. of nitrogen (3.75 Gm. of protein) per Kg. of body weight. The protein requirement also varies with the degree of depletion. Elman has outlined a practical method for determining the protein requirements of depleted patients, based on the experimental work of Weech.[11] Elman's assumptions are as follows: (1) The normal plasma albumin value is 4.5 Gm. per cent; (2) the normal plasma volume is one-twentieth of the actual body weight; (3) the loss of 1 Gm. of plasma albumin is equivalent to the loss of 30 Gm. of tissue protein; (4) about 50 per cent of the ingested protein will be utilized and (5) 25 Gm. of protein are used for maintenance daily. The further assumption may be made that the total plasma protein deficit may be used as a criterion of depletion in those patients in whom it is not possible to obtain albumin values, since albumin usually comprises the bulk of the plasma proteins lost.[11] In this calculation a normal value of 7 Gm. per cent is assumed. The figures obtained from these calculations apply only to certain types of protein depletion and are at best only a rough guide for replacement therapy.

They will, however, fulfill the important service of illustrating that in most cases the amounts of protein needed are actually of a larger magnitude than is often realized. For example, a patient weighing 60 Kg. with a plasma protein of 5 Gm. per 100 ml. would have to be given 3,500 Gm. of protein to restore his tissue protein deficit. Twenty-five Gm. of protein would have to be added daily for maintenance while protein stores are being replenished.

Careful evaluation of a protein hydrolysate includes consideration of the biologic value of the original protein that was hydrolyzed, the bacterial purity and the lack of toxicity of the final compound.

In some commercial preparations, palatability is improved by the addition of salt. This may result in toxic doses of sodium chloride when enough of such a preparation is given to provide the full nitrogen requirement in the postoperative phase.

A study of the chemical composition of some protein hydrolysates now commercially available has shown that the information given on the manufacturers' label is often incomplete and that the methods by which it is obtained are not standardized. The importance of such factors and the inadequacy of present standards for protein hydrolysates have previously been discussed.[12]

DISCUSSION AND SUMMARY

The use of protein hydrolysates should be limited to cases with clearcut indications such as have been outlined in the preceding paragraphs. They should be employed with full consideration of the physiologic implications of the use of such products. There is a wide variation in the composition of commercially available protein hydrolysates so that whenever large quantities are necessary a judicious choice of product is essential to avoid possible deleterious effects.

REFERENCES

1. Elman, R. Parenteral Alimentation in Surgery. New York, 1947. Paul B. Hoeber, Inc.
2. Stare, F. J. and Thorn, G. W. Protein nutrition in problems of medical interest. *J. A. M. A.*, 127; 16: 1,052–1,055, 1945.
3. Lewis, J. H., Taylor, F. H. L. and Davidson, C. S. Protein nutrition. *New England J. Med.*, 236; 10: 351–359, 1947.
4. Cohen, P. P. The metabolism of proteins and amino acids. *Ann. Rev. Biochem.*, 14: 357–382, 1945.
5. Co Tui. Personal communication.
6. Co Tui. Unpublished data. The Laboratory of Clinical Investigation, Sloan-Kettering Institute for Cancer Research, New York, N. Y. Unpublished data.
7. Mulholland, J. J., Co Tui, Wright, A. M. and Vinvi, V. Y. Studies on surgical convalescence: source of nitrogen loss post-gastrectomy and the effect of high amino acid and high caloric intake on convalescence. *Ann. Surg.*, 120: 99–122, 1944.
8. Co Tui. Personal communication.
9. Lund, C. C. and Levenson, S. M. Proteins in surgery. *J. A. M. A.*, 128; 2: 95–100, 1945.
10. Sherman, H. C. Chemistry of Food and Nutrition. New York, 1941. The Macmillan Co.
11. Weech, A. A., Wollstein, M. and Goettsch, E. Nutritional edema in the dog. *J. Clin. Investigation*, 16: 719–728, 1937.
12. Homburger, F. and Young, N. F. Chemical evaluation and labelling of protein hydrolysates for human consumption. *Am. J. Med.*, 3: 427, 1947.

Review

Contributions of Right Heart Catheterization to the Physiology of Congestive Heart Failure*

DICKINSON W. RICHARDS, JR., M.D.
NEW YORK, NEW YORK

THE determination of cardiac output in man by the "direct Fick" principle and the registration of pressures in the heart and great vessels through the technic of right heart catheterization[1–4] have added significantly to the knowledge of the physiology of the human circulation, both normal and abnormal. This field is now under active investigation, with new observations constantly being made and ideas changing. It may be of interest, however, to review some of the work that has been done during the last five years and consider some of the points of view that have been developed. The present discussion will compare the normal circulation with that in congestive heart failure: first, with respect to pressure relations in the systemic and pulmonary circuits;[5] second, with respect to total blood flow or cardiac output. Finally, these findings will be considered in relation to Starling's law.

The first of the facts to be established about the venous circulation in congestive heart failure through the catheterization technic was that the pressure gradient of 3 mm. or 4 mm. Hg which exists in the normal circulation between the peripheral (arm) vein and right auricle diminishes as soon as the venous pressure begins to rise in right-sided failure, and peripheral and central pressures then become and remain equal as the congestive state progresses.[6,7] This, as shown later by Ryder, Molle and Ferris,[8] is due largely to the change in peripheral veins from the partially collapsed to the filled and distended state.

More detailed study of pressures in the great veins and right side of the heart, especially in relation to the events of the cardiac cycle and respiration, became possible with the application of pressure recording through the use of the Hamilton manometer.[5]

Figure 1 shows a series of normal tracings recording by optical registration: (1) the electrocardiogram, (2) femoral artery pressure (by a Hamilton manometer connected to an indwelling arterial needle) and (3) intracardiac pressures. Section A shows a right auricular pressure tracing; Section B, in its first half, shows a right ventricular tracing and Section C shows a right auricular tracing during moderately increased respiration, also an intrapleural recording of pressure changes during respiration.

The events of the cardiac cycle, as re-

* From the Department of Medicine, Columbia University College of Physicians and Surgeons and the Cardiopulmonary Laboratory, Chest Service, Bellevue Hospital, New York, N. Y. The material in this paper is taken largely from a lecture delivered at the Centennial Symposium, University of Buffalo Medical School, October 2, 1946. The research studies from the Cardiopulmonary Laboratory, Bellevue Hospital, were supported by a grant from the Commonwealth Fund.

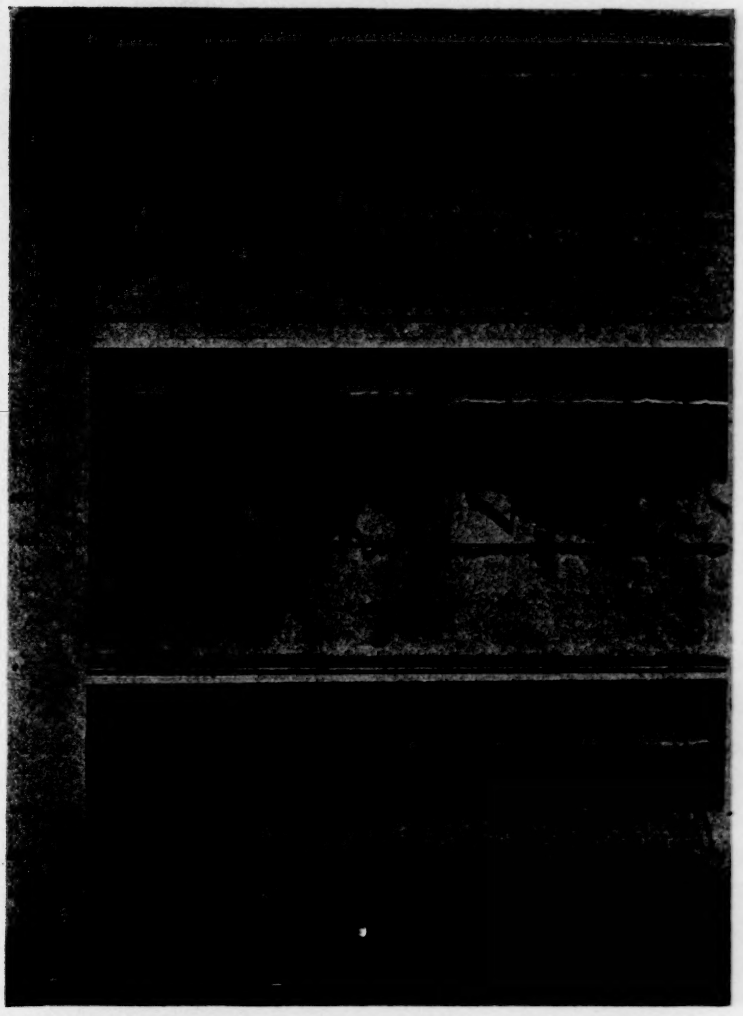


FIG. 1. Pressure tracings from normal human subjects. In Section A are recorded, from above downward, the electrocardiogram, arterial pressure tracing and right auricular pressure tracing. In Section B, electrocardiogram, arterial pressure and right ventricular pressure. At the arrow, the catheter tip was withdrawn from ventricle into auricle. In Section C, electrocardiogram, arterial pressure, intrapleural pressure (inspiration down, expiration up), right auricular pressure, during moderately increased respiration. The patient had a partial artificial pneumothorax.

corded in the right auricle, are indicated by the numbered lines. (Fig. 1, Section A.) At Line 1, auricular systole begins, producing a pressure 2 or 3 mm. Hg above the base line. Line 2 marks the onset of right ventricular systole, the slight upward notch in the pressure tracing probably indicating either bulging backward of the tricuspid valve or a momentary tricuspid insufficiency.[5] At Line 3 a drop in auricular pressure begins due to "descent of the base" of the heart, the heart moving footward with the ejection of blood headward; the auriculoventricular valve region moving toward the apex because of this motion and also because of ventricular contraction. Through the remainder of the ventricular systole and early relaxation, pressure in the right auricle builds up slowly as blood comes in from the great vessels. At Line 4 ventricular relaxation has reduced

pressure within this chamber to that of the auricle, the tricuspid valve opens with a drop in the auricular pressure as blood pours into the ventricle. From this point pressure builds up again gradually in the common auriculoventricular chamber, until the next auricular systole starts a new cycle.

As indices of the nature of blood flow in the great veins these tracings show that in the normal circulation under conditions of rest: (1) the basic pressure level is around zero (referred to atmospheric pressure); (2) the total pressure *change* during the cardiac cycle is small, about 5 mm. Hg. The fact that the great veins lose 70 or 80 cc. of blood with each ventricular filling and with so small a pressure change, indicates an ample venous reservoir under low tension.

Pressure in the right ventricle (Section B) usually shows a small rise due to auricular systole. Ventricular contraction then begins and maximum pressure is achieved rapidly. Since the normal diastolic pressure in the pulmonary artery is low, from 4 to 8 mm. Hg (as has been demonstrated with the catheter tip in the pulmonary artery[5]) the greater part of right ventricular systole is occupied with ejection of blood rather than with isometric contraction. Systolic pressure in the right ventricle (and in the pulmonary artery) in normal subjects varies from 18 to 30 mm. Hg and is on the average about 25 mm. Hg. The coarse vibrations in the tracings during the peak of systole (Fig. 1, B) are quite variable from one subject to another and may be artefacts. Right ventricular relaxation is also rapid, ending after opening of the tricuspid valve, in a small "diastolic dip," in which the pressure drops below the mean venous base line. After this, as already indicated, pressure builds up gradually in the common auriculoventricular chamber until the next auricular systole.

Figure 1, Section C shows the definite although small changes that occur in right auricular pressure tracings during moderately increased breathing. The base line changes, although to a lesser degree than does the simultaneously recorded intrapleural pressure. The auricular pressure waves during the cardiac cycle also are greater during inspiration and less during expiration. A further study of this has been made with right ventricular and arterial pressure tracings by Lauson, Bloomfield and Cournand.[9] Figure 2 gives the results in schematized form. It is found regularly in normal subjects that with inspiration right ventricular pulse pressure increases and femoral arterial pulse pressure diminishes. The reverse takes place during expiration. Furthermore, as already noted, the intrathoracic (intrapleural) pressure in inspiration decreases more than does the right intra-auricular or diastolic right intraventricular pressure. Thus the effective or net filling pressure on the right side of the heart is relatively increased. During expiration, intrathoracic pressure increases more than right intra-auricular pressure and net filling pressure is thus diminished.

If, as seems probable, these changes are responses to alterations in the volume flow of blood rather than vasomotor activity, then it can be calculated that with each inspiration more blood flows into the lungs from the right ventricle and less flows out of the lungs into the left auricle and ventricle; with the opposite changes in expiration. There are in some subjects small alterations in pulse rate with respiration but these do not significantly affect the general relation above stated.

The lungs thus act as a sponge in this dynamic equilibrium, taking in additional blood during inspiration and expelling it during expiration, a function clearly described many years ago by Thomas Lewis[10] and by Sahli.[11]

If one modifies the principle of Starling's law to the extent of assuming that systolic output varies with diastolic filling pressure

in the ventricles (rather than with diastolic volume), then this respiratory equilibrium conforms with Starling's law.[12]

Additional evidence in favor of this explanation of the changes in right and left heart performance during respiration is provided by the reverse effects noted during artificial respiration with a positive pressure respirator, as described by Motley et al.[13] Inspiration produced by inflow of air under positive pressure results in a decrease in net filling pressure in the right heart with lowered right ventricular pulse pressures, while at the same time arterial pulse pressures increase, suggesting increased left ventricular systolic output. In (passive) expiration, right-sided net filling pressure and right ventricular pulse pressure increase while arterial pulse pressures decrease.

Pressure tracings from the great veins and chambers of the right heart in congestive failure present an interesting contrast to the normal records. It should be emphasized at this point that we are now dealing with the phenomena of established failure and are not concerned with the mechanisms of its progressive development.

Figure 3, Section A, gives records of right intra-auricular and intraventricular pressures in a case of pure right-sided failure, specifically, a patient with constrictive pericarditis. It will be seen first, as one would expect, that the venous or right auricular pressure level is high, about 20 mm. Hg. In addition, the variations of pressure in the auricle during the cardiac cycle are much greater than in the normal subject, being as much as 15 mm. Hg. There are two sharp drops in pressure, one with the "descent of the base" at the time of ventricular ejection, the other with the opening of the tricuspid valve and inflow of blood from the auricle to the ventricle. Thus the pressure curve in the conjested right auricle has a typical "W" contour. The whole response is what one might anticipate in a distended elastic vessel, with relatively small changes in volume producing large changes in pressure.[8]

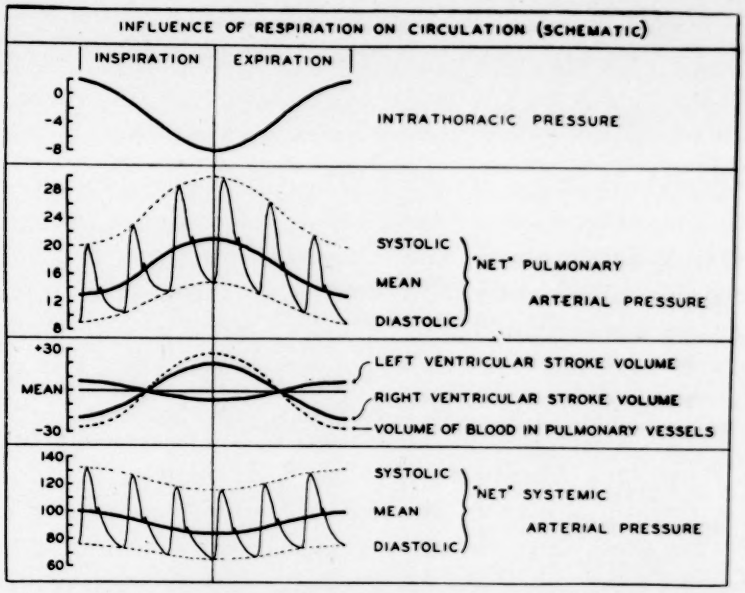


FIG. 2. (From Lauson, Bloomfield and Cournand.[9]) Schematized representation of right ventricular and arterial pressures as affected by respiration. With inspiration, right ventricular pulse pressures increase while femoral pulse pressures diminish; in expiration, the reverse occurs.

FIG. 3. Arterial, right auricular, and right ventricular pressure tracings in a patient with right-sided congestive failure (patient had constrictive pericarditis).

As already mentioned, in cases of well marked right-sided congestion such as this one, mean pressures in the right auricle and peripheral veins are essentially identical. In fact, close measurement shows that during late ventricular systole and late auriculo-ventricular diastole, pressure in the right auricle is actually slightly above that in the peripheral (arm) vein[5] and blood must, therefore, either be drifting slowly in the reverse direction in the great veins, or else a higher inflow pressure from other venous sources must be filling the right auricle with closure of the axillary venous valves.[14] During the two sharp drops of the "W" there is an abrupt change of direction with a flow toward the heart.[5]

In Figure 3, Section B, the tracing of right ventricular pressure in the same case of constrictive pericarditis is shown. The systolic pressure is normal, there being in this case no disturbance in the lesser circuit. Diastolic ventricular pressure is, of course, high and equal to auricular and peripheral venous pressure. A special feature is the marked ventricular "diastolic dip" as the ventricle relaxes just after the tricuspid valve opens, with a rapid rise again to its previous level. The explanation of this is the same as that of the second dip in the "W" curve of the right auricle.

Left-sided congestive heart failure produces greatly elevated pressures in the lesser circuit and the right ventricle. The degree of hypertension in the pulmonary circuit is seen in Figure 4, Sections A and B, a case of rheumatic heart disease with mitral stenosis and insufficiency and tricuspid insufficiency in advanced congestive failure. The right auricular tracing shows the high level of venous pressure and the large variations of pressure during the cardiac cycle already mentioned. The first dip of the "W" curve is absent in this case because of the tricus-

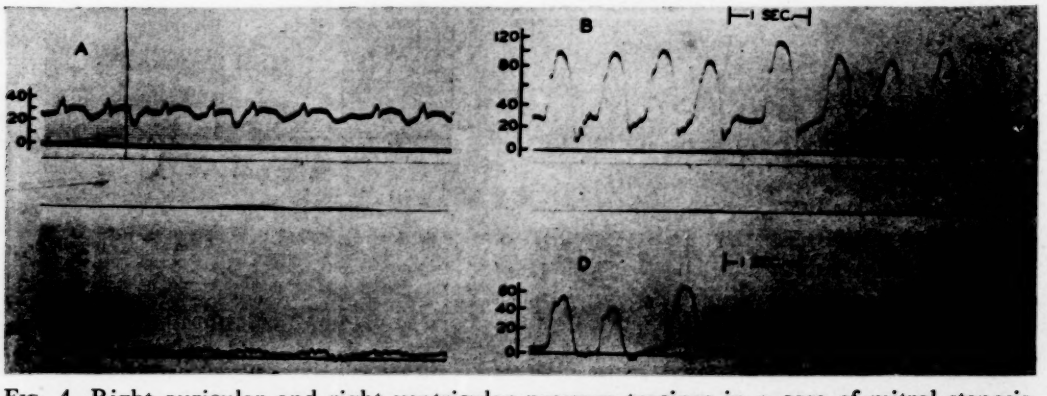


FIG. 4. Right auricular and right ventricular pressure tracings in a case of mitral stenosis. Sections A and B during congestive failure; Sections C and D after recovery of compensation.

FIG. 5. Pressures in right ventricle (above) and in pulmonary artery (below), in a patient with rheumatic heart disease in left-sided and right-sided congestive failure. The tracings were taken simultaneously by the use of a double-channel catheter. The recording membrane for the pulmonary artery pressure tracing is slightly more sensitive than that for the right ventricle.

pid insufficiency.[5] Auricular systole is absent and the heart rate irregular since the auricles were fibrillating.

Even more striking, however, is the right ventricular tracing, with systolic pressures up to 100 mm. Hg. Figure 5, a record of pulmonary artery pressure taken from another case with the catheter tip in the pulmonary artery, shows that the diastolic as well as the systolic pressure in this vessel is elevated. This four-fold increase in systolic pressure in the lesser circuit demonstrates beyond any question that hypertensive congestion in the lesser circuit is the dominant factor in left sided congestive failure, thus confirming the *Lungenstarre* postulated by von Basch more than sixty years ago.[15]

In Figure 4, Sections C and D, tracings of the same patient after digitalization and partial recovery of compensation are reproduced. It will be seen that the systemic venous pressure has returned to normal. The pulmonary arterial hypertension is less but the systolic pressure in the lesser circuit is still about twice normal.

In cor pulmonale, or right sided cardiac hypertrophy associated with chronic pulmonary disease, pulmonary arterial hypertension is an important factor but it is interesting that the degree of this hypertension is usually less than that seen in left heart failure of the congestive type.[5] There is, however, an additional disturbing factor caused by the loss of pulmonary elasticity. In Figure 6 arterial and right ventricular pressure tracings in a group of patients with emphysema and various forms of chronic fibrotic pulmonary disease are shown. Section A is from a patient with emphysema. The variations of auricular pressure due to inspiration and expiration are somewhat greater than the normal range but there is no right ventricular or pulmonary hypertension. In nineteen cases of emphysema studied by Bloomfield et al.,[5] five had normal right ventricular pressures. The other tracings in Figure 6 illustrate increasingly severe degrees of chronic fibrotic pulmonary disease with cor pulmonale. None of these patients, however, were in right sided congestive failure. In addition to pulmonary arterial hypertension there will be noted, as pulmonary elasticity becomes impaired and ventilatory effort increased, a progressive exaggeration of the normal respiratory pressure effects on inflow and outflow of blood to and from the lungs. The basic levels of venous pressure shift widely with

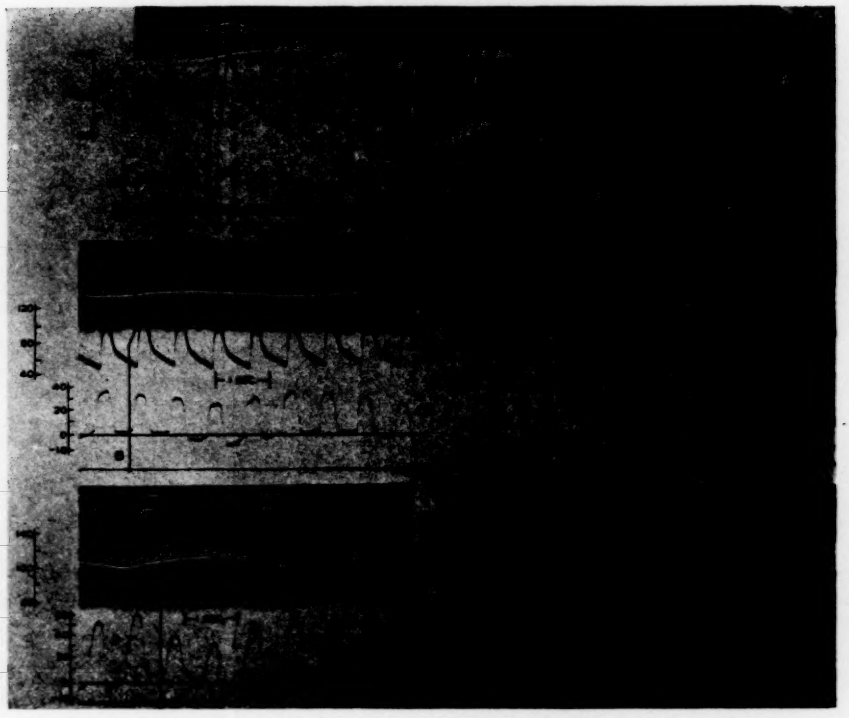


FIG. 6. Arterial (middle curves) and right ventricular (lower curves) pressure tracings in five subjects with pulmonary emphysema and varying degrees of pulmonary arterial hypertension. The white lines above are records of respiration: inspiration down, expiration up.

respiration, as do the amplitude of right ventricular pressures and femoral arterial pulse waves, indicating alternate filling and emptying of the pulmonary vascular bed with inspiration and expiration. Whether this imposes a further strain on cardiocirculatory function cannot be said with certainty but it seems not unlikely. It might be noted that patients with left heart failure and pulmonary engorgement may also show these marked respiratory variations in intracardiac pressures.

Rist[16] noted a relative decrease in amplitude of cardiac systole during inspiration in such patients but explained the effect as a decrease in inspiratory systolic outflow of both right and left ventricles, associated with a rigid pulmonary vascular bed. It is suggested that the change in amplitude of the heart shadow, as observed by Rist, may have been largely due to the left ventricle and that while the pulmonary vascular bed in these cases may be less elastic than normal, it is relatively more elastic than the pulmonary parenchyma so that the exaggerated effort of inspiration and expiration produces alterations in vascular volume that are greater than normal.

In cor pulmonale with right-sided congestive failure the pressure changes in great veins and right heart chambers during the cardiac cycle are similar to those already described.

All the above evidence taken together gives emphasis to the importance of pressure disturbances in both systemic and pulmonary circulations in congestive heart failure.

Turning now to a consideration of total blood flow or cardiac output, one may present the essential findings briefly.

In normal adult subjects at rest, the average cardiac output as determined by the catheterization procedure is about 3.1 liters per square meter of body surface per minute,

or 5.4 liters per minute for an individual of average size.[1] As was demonstrated by earlier technics (Grollman[17]) cardiac output is an extremely labile function, often changing markedly with nervousness or anxiety.[1]

The response in normal subjects to rapid increase in venous inflow by intravenous infusion and the response to reduced venous inflow by venesection or by applying venous cuffs to the extremities have been variously reported. According to McMichael and Sharpey-Schafer,[1] cardiac output is regularly increased in proportion to the increase in inflow pressure or pressure in the right auricle, and correspondingly decreased as the right auricular pressure decreases with venesection or venous cuffs. Warren, Brannon, Stead and Merrill, however,[18] in similar experiments, have not found this correlation and believe that in normal circulations alterations in cardiac output may be independent of pressure in the right auricle (i.e., diastolic filling pressure in right auricle and right ventricle).

TABLE I
PATIENT A. R. ARTERIOSCLEROTIC HEART DISEASE, HYPERTENSION AND PROGRESSING CONGESTIVE HEART FAILURE

Date	9/21/43	1/18/44
Cardiac index, liters	2.33	2.01
Stroke volume, cc	44	30
Arteriovenous difference, cc./100	5.2	7.4
Arterial blood pressure, mm. Hg	154/89	190/129
Peripheral resistance	2570	3335
Auricular pressure, mm. H_2O	+24	+140
Arm venous pressure, mm. H_2O	+35	+135
Right ventricular pressure, mm. Hg	27/4	64/18
Plasma volume, cc./sq. m	1420	1620
Hematocrit	40	40
Total blood volume, cc./sq. m	2370	2700

Since Starling's law states that the energy of systolic ejection of the heart varies with diastolic filling or diastolic size, it is of interest to inquire how the heart size changes with increased output. McMichael[19] has shown a definite increase in the cardiac area by x-ray during a rapid intravenous infusion, associated with increased output.

In muscular exercise, on the other hand, Nylin's recent work[20] indicates that increased stroke volume is achieved wholly by increased emptying of the heart chambers, the cardiac size being smaller than when at rest. Measurements of cardiac output during exercise, by the catheterization technic, are in progress in several laboratories but have not yet been published.

The subject of cardiac output in congestive heart failure has been extensively studied, both before and since the introduction of right heart catheterization. Harrison, in his important monograph published in 1935,[21] summarized previous investigations and added evidence from his own experiments, indicating that decrease in cardiac output is not present early in the development of congestive heart failure. The validity of this position is now being examined again with the catheterization technic.

In patients with fully established congestive failure, however, the following facts have recently been established, both in Cournand's laboratory[22] and by McMichael and his group:[23]

(1) There are some types of congestive failure regularly associated with decrease in cardiac output, notably arteriosclerotic heart disease and rheumatic heart disease. Table 1 gives figures in a typical case of the former, first in mild failure and later when cardiac insufficiency was advanced. The cardiac index, or cardiac output in liters per minute per square meter of body surface, was in this case well below the average normal value of 3.1, and fell still further with further decompensation.

(2) There are other forms of congestive heart failure associated with a normal or increased cardiac output, even when the congestive state is marked. In such clinical conditions there is usually some metabolic

or mechanical dysfunction which induces or stimulates the increased output. These conditions and their corresponding metabolic dysfunctions are as follows:

(1) Anemia (low oxygen transport per unit of blood); (2) cor pulmonale (usually a low arterial and tissue oxygen tension); (3) thyrotoxicosis (increased oxygen consumption); (4) arteriovenous communications (increased venous return); (5) Paget's disease (essentially arteriovenous communications in vascular bed of affected bones); and (6) in addition, Burwell et al.,[25] have recently shown a very large cardiac output (11 liters per minute) in a case of beriberi heart disease in marked congestive failure.

Table II gives average figures of cardiac output and other functions in a series of cases of cor pulmonale, compared with similar measurements in cases of rheumatic heart disease, both groups of patients being in congestive failure.

These clearcut findings would seem to lead to an equally definite conclusion; that in the state of established congestive heart failure, cardiac output may be high, low or normal, or to put it otherwise, that a lowered cardiac output is not an essential feature of this condition.

Before this conclusion can be accepted, however, there are two prior questions which have been raised in other discussions of these findings and should be considered:

(1) Can one say that a state of cardiac failure exists at all, so long as cardiac output is maintained?

TABLE II

MEASUREMENTS OF THE CIRCULATION IN A GROUP OF SEVEN PATIENTS WITH RHEUMATIC HEART DISEASE IN FAILURE AND IN A GROUP OF SIX PATIENTS WITH COR PULMONALE IN FAILURE

	Rheumatic		Cor Pulmonale	
	Average	Range	Average	Range
Cardiac index, liters	1.85	(1.21–2.65)	3.45	(2.59–4.88)
A-V difference, cc./100	8.1	(6.4–11.4)	4.6	(3.4–5.9)
Peripheral resistance	2562	(1710–3720)	1342	(1100–1510)
Auricular pressure, mm. H_2O	+240	(167–350)	+114	(−24 to +180)
Venous pressure, mm. H_2O	+245	(173–320)	+126	(−15 to +222)
Ventricular pressure, mm. Hg	100	(81–117)	53	(35–81)
Plasma volume, cc./sq. m.	2574	(1630–3370)	1685	(1400–1860)
Hematocrit	45	(36–53)	63	(54–69)
Arterial O_2 saturation, %	95	(90–98)	71	(61–85)

(2) In cases of the congestive state with cardiac output at levels that are normal or above, to what extent is the congestion in its various aspects compensatory, maintaining cardiac output higher than it would otherwise be, to the benefit of the individual?

These are essentially different aspects of the same question, the first being an extreme or limiting case of the second.

It ultimately becomes a matter of terminology as to whether the advanced congestive state with normal cardiac output shall be called heart failure or not. It is difficult to see, however, why it should not be so called. The state of the heart, emptying inadequately, greatly dilated and under excessive filling pressures, is certainly one of profound distress. Furthermore, if the condition continues to progress, failure becomes complete and the patient dies. Surely this is a form of heart failure. It happens to be failure in terms of pressure relations rather than of flow relations.

These recent observations, in fact, do not

alter Harrison's excellent description in his monograph of 1935,[21] of the development of the congestive state with incipient failure of cardiac emptying, then dilatation, this resulting in maintained cardiac output, then further failure of emptying with increased diastolic (i.e., venous) pressure and so on through the successive steps of decompensation. Clinically, one should look for the onset of true heart failure earlier rather than later in this train of events.

Since the constant disturbances in congestive heart failure are those of pressure rather than of flow, the term "congestive" is both appropriate and adequate. One may question, however, whether the terms "backward" and "forward" failure are any longer useful or accurate. It is true that the cardiac chambers are dilated in failure and that inadequate emptying of these chambers is a part of, if not a cause of, the general state of venous congestion, but if blood is still moved around the circuit in a normal amount the condition is not backward failure from the point of view of flow. If it is backward failure from the point of view of pressures only, then we have simply returned to the status of congestion, from which our argument started.

It is perhaps not too much of a digression to note that the term forward failure, to describe states of shock due to peripheral circulatory failure, also becomes difficult to apply satisfactorily, in view of present knowledge of the circulation in different forms of shock.[26] Is the forward failure a failure of blood flow or of pressure? There are states of shock with low blood flow and low arterial pressure (trauma and blood loss), others with low blood flow and normal or increased arterial pressure (burns) and still others with normal blood flow and low arterial pressure (syncope). All, however, are associated with inadequate filling of one or another part of the system of heart and great vessels. Perhaps, instead of forward versus backward failure, better descriptive terms would be depletion versus congestion of all or part of the system: veins plus heart plus arteries.

The question already presented above as to whether the congestive state may at times

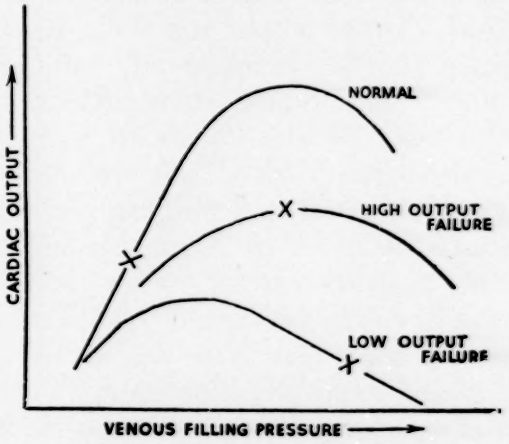


FIG. 7. (From Howarth, McMichael and Sharpey-Schafer.[14]) Suggested filling pressure-cardiac output curves for normal subjects and cases of high and low output failure. Crosses represent usual states of each group at rest.

be a favorable compensatory mechanism, demands a critical review of the physiologic principle upon which modern ideas of cardiac output rest, namely, Starling's law, and the extent of its applicability to the human circulation in the light of these recent observations. In its most simple terms this law (derived from studies with the heart-lung preparation of the dog) states that the energy of cardiac ejection (or output) increases in proportion to the length of the heart muscle fibers, in other words, to the diastolic volume of the heart chambers; up to a certain degree of filling, beyond which further overfilling results in decrease rather than increase in cardiac output. The upper curve in Figure 7, from the recent paper by Howarth, McMichael and Sharpey-Schafer[23] gives the essential relation, although using diastolic filling pressure rather than diastolic volume as the abscissa.

To what extent does the normal circulation obey Starling's law? McMichael's data on intravenous infusions and venesection,[1] are consistent with the law, cardiac output increasing along with increased filling pressure and increased heart size. On the other hand, in muscular exercise although venous pressure, cardiac output and stroke volume increase, cardiac size apparently diminishes (Nylin[20]). Stead's data on venesection and anxiety states[1,18] also do not fit Starling's law. McMichael[1] has at least one observation that does not; epinephrine given intravenously in doses of 3 micrograms per minute increases cardiac output with no change in venous pressure or pulse rate. In favor of Starling's law is the well known fact that during severe physical training, such as that of oarsmen training for a race, cardiac size increases.

Apparently, therefore, while there is a tendency in the normal circulation to follow Starling's law, there are also influences of nervous or metabolic origin which may alter such functions as cardiac tone (diastolic heart size at a given inflow pressure) or systolic emptying and thus modify cardiac performance outside this law.

There are other influences acting in the same manner. The increased blood flow, for example, seen in anxiety states, fever, moderate thyrotoxicosis or anemia *without* congestive failure usually occurs with both normal venous pressures and little or no increase in heart size and is thus dependent on mechanisms other than those of Starling's law.

Whether normal hearts pushed to the point of failure dilate with falling output (Fig. 7) is not certainly known but such is probably the case. Extreme overexertion is known to produce cardiac dilatation in normal subjects.

There is abundant evidence, however, that the heart in congestive failure that has a low output occupies a position indicated by the "low output failure" in Figure 7. The heart is dilated, the venous pressure is high and the output is low.[23] Proof that such a heart is overdilated, that it is on the descending limb of the curve (mark "X" on the lowest curve), is given by the fact that decrease of venous pressure, as by cuffs, digitalis or phlebotomy produces prompt increase in cardiac output.

The low level of cardiac output at which these hearts are operating, as compared with the normal, is presumably associated with the fact that for the most part these are hearts with intrinsic myocardial damage.

Is it also true that these hearts were at an earlier stage on the rising side of the curve when increased venous pressure and increased diastolic volume were associated with a favorable compensatory increase in cardiac output? It is difficult to answer this question. Clinically, cardiac dilatation is usually considered an unfavorable event and the sooner it is reduced the better the clinical result. In any case, as in so many forms of compensation in a failing organ, the compensation soon becomes unfavorable. In this instance abnormal pressure relations become a greater handicap than the increased cardiac output is a benefit and all the evils of congestive failure supervene.

The cases of "high output failure," represented by the middle curve in Figure 7, bring forward more clearly the question of a compensatory state of congestion. In the cor pulmonale group, for example, it is McMichael's suggestion that the venous pressure elevation and correspondingly increased diastolic filling has increased the cardiac output to a maximum (point "X" on the curve). In support of this he notes that digitalis decreases both venous pressure and cardiac output in such hearts and is known to be an ineffective drug clinically.

On the other hand, the lowering of venous pressure may not be unfavorable in such patients. Table III, for example, gives figures

in a case studied by Cournand of cor pulmonale in right heart failure, in which a normal cardiac output was further increased after phlebotomy and the patient dramatically improved. In general it has been our experience that patients with cor pulmonale

TABLE III
CARDIAC OUTPUT BEFORE AND AFTER A PHLEBOTOMY OF 1,200 CC. IN A PATIENT WITH COR PULMONALE AND CONGESTIVE HEART FAILURE

Patient M. K., 10/5/42	Before Phlebotomy	Immediately after	Three Hours after
Pulse rate	92	93	97
Venous pressure, mm. H_2O	185	84	
Right auricular pressure, mm. H_2O	185	64	115
Arterial pressure, mm. Hg	154/100	137/82	133/81
Arterial oxygen saturation, %	61	73	60
A-V oxygen difference, cc	49	44	41
Cardiac index, lit./min./sq. m.	3.1	3.4	4.0
Plasma volume, cc	3310	.....	3100
Hematocrit, %	68		63

in right-sided congestive failure have large blood volumes and are greatly improved by repeated venesections. In our patients, therefore, while cardiac output is high in the presence of venous congestion the latter is still a phenomenon of failure and its relief results in an improved circulation.

There is also the evidence (Sharpey-Schafer[27]) in favor of a compensatory increase in blood flow due to venous pressure increases in patients with severe anemia and congestive failure. It should be noted, however, that severe anemia regularly causes increased cardiac output, even without venous pressure increase;[28] also that normal hearts can increase cardiac output as high as it occurs in anemia without the development of congestion. Therefore, when the congestive state develops in anemia, even if it is compensatory, it is the compensating response of a failing heart and not the response of a normal heart.

By way of summary, so far as concerns the application of Starling's law to the human circulation, the following comments are suggested:

(1) In normal subjects, in certain restricted measurements under controlled conditions, a relation at least between cardiac stroke volume and diastolic filling pressure can be demonstrated in accordance with Starling's law; (2) in other physiologic situations, such as exercise, anxiety, etc., other influences affect cardiac performance outside the scope of Starling's law and (3) in congestive heart failure, the law does apply in the "failure" range or descending segment of the curve, with cardiac output increasing as venous pressure and heart size are diminished.

Starling's law, in fact, applies to the human circulation about as well as one could expect of a physiologic principle developed from the performance of a heart-lung preparation; the more the human heart is exposed to and reacts to nervous, vasomotor and metabolic influences the less it behaves in accordance with this law; the more the heart fails to respond to such influences and becomes simply a pressure-volume muscle preparation, as in congestive failure, the more closely it follows the law.

From this point of view, Starling's law becomes a useful but not exclusive and not always dominant principle to be considered in the interpretation of normal and abnormal circulatory states. One further comment might be made, namely, that the current practice of describing Starling's law as a relation between cardiac output and diastolic filling pressure may prove to be more useful than the original law which states the relation between cardiac output and diastolic heart volume. If cardiac tonus is an important factor, the relation to diastolic filling pressure may even be more accurate.

A number of important studies have been made with the catheterization procedure of

other aspects of congestive failure—the early development of the congestive state, the relation of renal blood flow, and the action of digitalis and other drugs on the heart and peripheral circulation. These are outside the restricted scope of the present discussion.

SUMMARY

1. Some observations are presented of intravascular and intracardiac pressures, and of cardiac output in subjects with normal hearts and in patients with congestive heart failure, as obtained by the technic of right heart catheterization.

2. The phenomenon of congestive heart failure is essentially a disturbance of pressures rather than of blood flow.

3. There appear to be limitations in the applicability of Starling's law to functioning human hearts.

REFERENCES

1. Cournand, A., Riley, R. L., Breed, E. S., Baldwin, E. deF. and Richards, D. W., Jr. Measurement of cardiac output in man using the technique of catheterization of the right auricle or ventricle. *J. Clin. Investigation*, 24: 106, 1945.
2. Stead, E. A., Jr., Warren, J. V., Merrill, A. J. and Brannon, E. S. The cardiac output in male subjects as measured by the technique of right atrial catheterization. Normal values with observations on the effect of anxiety and tilting. *J. Clin. Investigation*, 24: 326, 1945.
3. McMichael, J. and Sharpey-Schafer, E. P. Cardiac output in man by a direct Fick method. *Brit. Heart J.*, 6: 33, 1944.
4. Cournand, A., Lauson, H. D., Bloomfield, R. A., Breed, E. S. and Baldwin, E. deF. Recording of right heart pressures in man. *Proc. Soc. Exper. Biol. & Med.*, 55: 34, 1944.
5. Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S. and Richards, D. W., Jr. Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardiocirculatory disease. *J. Clin. Investigation*, 25: 639, 1946.
6. Richards, D. W., Jr., Cournand, A., Darling, R. C. and Gillespie, W. H. Pressure in the right auricle of man, in normal subjects and in patients with congestive heart failure. *Tr. A. Am. Physicians*, 56, 218, 1941.
7. Richards, D. W., Jr., Cournand, A., Darling, R. C., Gillespie, W. H. and Baldwin, E. deF. Pressure of blood in the right auricle, in animals and in man: under normal conditions and in right heart failure. *Am. J. Physiol.*, 136: 115, 1942.
8. Ryder, H. W., Molle, W. E. and Ferris, E. B., Jr. Influence of the collapsibility of veins on venous pressure, including a new procedure for measuring tissue pressure. *J. Clin. Investigation*, 23: 333, 1944.
9. Lauson, H. D., Bloomfield, R. A. and Cournand, A. The influence of the respiration on the circulation in man with special reference to pressures in the right auricle, right ventricle, femoral artery and peripheral veins. *Am. J. Med.*, 1: 315, 1946.
10. Lewis, T. Studies on the relation between respiration and blood pressure. *J. Physiol.*, 37: 212, 1908.
11. Sahli, H. Lehrbuch der klinischen Untersuchungsmethoden. Vienna, 1909.
12. Patterson, S. W., Piper, H. and Starling. E. H. The regulation of the heart beat. *J. Physiol.*, 48: 464, 1914.
13. Richards, D. W., Jr., Cournand, A. and Motley, H. L. Effects on circulatory and respiratory functions of various forms of respirator. *Tr. A. Am. Physicians*, 59: 102, 1946.
14. McMichael, J. Personal communication, suggested by unpublished observations by Sharpey-Schafer.
15. Von Basch, S. S. K. Die cardiale Dyspnoe und das cardiale Asthma. *Klin. Zeit. und Streitsfragen*, p. 82, 1887.
16. Rist, E. Les variations respiratoires de la systolique cardiaque et de la pression arterielle. *Arch. d. mal. du coeur*, 31: 477, 1938.
17. Grollman, A. The Cardiac Output of Man in Health and Disease. Baltimore, 1932. Charles C. Thomas.
18. Warren, J. V., Brannon, E. S., Stead, E. A., Jr. and Merrill, A. J. The effect of venesection and the pooling of blood in the extremities on the atrial pressure and cardiac output in normal subjects with observations on acute circulatory collapse in three instances. *J. Clin. Investigation*, 24: 337, 1945.
19. McMichael, J. Personal communication.
20. Nylin, G. On the amount of, and changes in, the residual blood of the heart. *Am. Heart J.*, 25: 598, 1943.
21. Harrison, T. L. Failure of the Circulation. Baltimore, 1935. Williams and Wilkins Co.
22. Richards, D. W., Jr. Cardiac output by the catheterization technique in various clinical conditions. *Federation Proc.*, 4: 215, 1945.
23. Howarth, S., McMichael, J. and Sharpey-Schafer, E. P. Effects of venesection in low output heart failure. *Clin. Sc.*, 6: 41, 1946.
24. McMichael, J. Circulatory failure. *Schweiz. med. Wchnschr.*, 37; 38: 851, 1946.
25. Burwell, C. S. and Dexter, L. Measurements of the circulation in beriberi heart disease. *Tr. A. Am. Physicians*, 1947 (in press).
26. Richards, D. W., Jr. The circulation in traumatic shock in man. The Harvey Lectures Series. 39: 217, 1943–44.
27. Sharpey-Schafer, E. P. Transfusion and the anemic heart. *Lancet*, 2: 296, 1945.
28. Brannon, E. S., Merrill, A. J., Warren, J. V. and Stead, E. A., Jr. The cardiac output in patients with chronic anemia as measured by the technique of right atrial catheterization. *J. Clin. Investigation*, 24: 332, 1945.

Seminars on Thromboembolism

Anticoagulation Therapy with Heparin/Pitkin Menstruum in Thromboembolic Disease*

LEO LOEWE, M.D.
BROOKLYN, NEW YORK

THE purpose of this report is to present experimental and clinical data regarding the rationale and effectiveness of heparin in the treatment of thromboembolic disease, and to describe in detail an improved and accepted method of prolonged heparinization which is safe, practical and simple.[1–8]

Heparin/Pitkin menstruum has been for a number of years the subject of elaborate clinical study and trial in the prophylaxis and treatment of intravascular thrombosis.[2, 3, 5, 6, 8, 9, 10, 11] Our composite series totals more than 400 patients who received several thousand subcutaneous deposits of heparin/Pitkin menstruum. Inasmuch as experimental study and clinical experience with this anticoagulation preparation has been more extensive in the field of venous thromboembolism, this division of thromboembolic disease will be considered in detail. The knowledge thus acquired has provided the basic principles which are applied in the treatment of arterial thrombotic diseases. The studies and investigations of anticoagulation therapy in arterial thrombotic disorders, some of which are still in the exploratory stage, will also be reviewed.

VENOUS THROMBOEMBOLIC DISEASE

Although much of the discussion on the functional pathology of venous thromboembolic disease has been published in previous papers,[3, 5, 12, 13] reiteration of certain basic information and findings is desirable if not indispensable. Despite the fact that thromboses in the calf and plantar veins were observed for many years and were not regarded as uncommon or rare, the relationship between these minimal thrombotic episodes and fatal pulmonary emboli has been emphasized only in the past decade. During this period the anatomic development of pulmonary emboli has been elucidated by Rössle,[14] Neumann[15] and Frykholm.[16] At the same time the clinical and radiographic criteria by which aseptic deep calf thrombi can be recognized even in their incipiency and prior to the occurrence of pulmonary embolization were established by Homans,[17] and Bauer,[18] Bancroft,[9] Ochsner,[20] Allen and his co-workers[21] and Bauer[22] during this same period defined the principles of treatment for pulmonary embolization based on functional anatomy and clinical pathology.

It is fitting at this point to trace the functional pathology of a venous thromboembolic accident, keeping in mind, however, there are many gaps in our knowledge of spontaneous intravascular clotting. Our interest in the genesis and nature of intravascular clots was stimulated during an investigation of experimental human frostbite.[12, 13] A study of the train of events in this condition by Greene[23] and Rotnes and

* From the Thromboembolic Disease Unit, the Department of Medicine and the Department of Laboratories, Jewish Hospital, Brooklyn, N. Y.

Kreyberg[24] revealed that there is clumping of erythrocytes in the dilated arterioles for at least seventy-two hours after exposure. This clumping has been attributed to loss of plasma through the highly permeable vascular wall. As a result the red cells are stranded, "silting" up the blood vessels and forming what may be termed a sludge. Related and revealing information on sludge development may be found in Knisely's report on this phenomenon in the blood during malaria and in traumatic shock.[25] He and his co-workers observed that the red cells become agglutinated and form small clumps as a result of which the blood flow becomes sluggish and generalized thromboses supervene.

Another related circumstance is the well established fact that the blood platelet count rises rapidly in the immediate postoperative period and that the platelets become hyperadhesive.[26,27] Both phenomena attain their maxima about the tenth day after operation. In addition to changes in the number and properties of the blood platelets and sludge formation, the postoperative period is characterized by variable hemoconcentration, enhanced viscosity of the blood plasma, hyperglobulinemia and an increased content of fibrinogen in the blood. Since all of these changes contribute to clot formation the stage is set for intravascular thrombosis anywhere in the body.

Even though all of the component elements for clot formation are present, the catalyzing circumstance which initiates the chain reaction eventuating in clot formation is still unknown. In a statistical review of phlebothrombosis one suggestive fact emerges: that a common denominator may be venostasis, whether due to angulation, actual obstruction or increased venous pressure secondary to either obesity or cardiac insufficiency. If one now considers what part of the body would be most subject to slowing of the blood stream, for self-evident reasons the lower extremities must rank first. Thus during the postoperative period, in the presence of chemical and physical changes in the blood, minimal intimal trauma in a venule of the lower extremity may well initiate local intravascular thrombosis.

The primary thrombotic process usually starts in the smaller vessels in the muscular portions of the calf and less frequently in the plantar veins. The clot progresses and soon reaches a larger vessel into which it extends and grows. At first the clot is attached only to the venule and later engages the wall of the larger vessel. During the stage of propagation it is, in the main, a red cell clot which waves freely in the vascular stream. This clot contains minute amounts of fibrin and is but one stage removed from the sludges observed in experimental frostbite and malaria.

The red cell clot has been produced by us in the laboratory;[4,7] a palpable, visible clot which, however, is so loosely put together that it disintegrates readily. As the clot grows the propagating proximal end includes all of the stages just described. It is now that the clot is most dangerous for it may separate at any time, either spontaneously or due to muscular exertion such as straining at stool or getting out of bed. If the clot does not become detached, it is slowly organized and becomes agglutinated to the blood vessel wall. During the stage of clot propagation, immediately adjacent tributaries and collaterals are also involved so that when organization with either obliteration or recanalization occurs, there is a shunting of the venous stream to superficial vessels incapable of bearing the burden. This bizarre venous shunting is readily seen in post-thrombotic phlebograms. (Fig. 1.) Although we have been discussing so-called aseptic phlebothrombosis, essentially the same processes occur in infective thrombophlebitis in which the

most proximal portion of the clot resembles the non-infective type despite the fact that the distal clot is for the most part attached to an injured intima.

If either the aseptic or septic type of thrombophlebitis be of prolonged duration, a periphlebitis occurs which involves the adjacent perivenous lymphatics. Since lymphatic fluid is also capable of coagulating it is quite conceivable that postphlebitic edema may be due in great part to consequent obstruction of the return lymphatic flow of an extremity.

Rationale. Termination of the progression of the thrombotic process is the ideal objective and, to the best of our present knowledge, the anticoagulants appear best suited for this purpose. The properties of heparin which render it uniquely applicable in thromboembolic disease are that it prevents (with the aid of a plasma co-factor) the conversion of prothrombin to thrombin; it forms with serum albumin a strong antithrombin and finally, it prevents the formation of thromboplastin from platelets. (Fig. 2.)

Heparin is a mucoitin polysulfuric acid. The most potent preparations of heparin, according to Jorpes,[29] contain 45 per cent sulfuric acid, which results in an exceedingly strong negative electric charge. No other compound of high molecular weight in the mammalian body has such a strong electric charge. Apparently heparin exerts its action through this charge. This seems to be supported by the neutralizing effect of basic protamine, which has the property of promptly counteracting the action of heparin. The multiple effect of heparin on thromboplastin, prothrombin, thrombin, the hemolytic complement, isohemagglutinins and different enzymes is most readily explained as a loading and unloading of electric charges on the proteins concerned. The properties of heparin predicate the fact that a clot, regardless of its site or stage, cannot propagate in the presence of heparin. However, what happens to the clot which is already present?

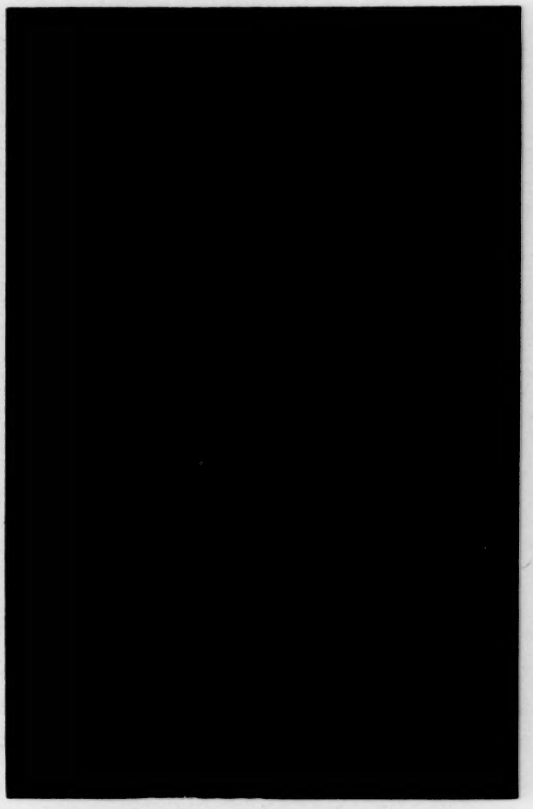


FIG. 1. Phlebogram taken five months following femoral thrombosis treated merely by paravertebral nerve block. Observe the failure of visualization of deep venous channels and the bizarre shunting to the superficial venous system due to the post-thrombotic occlusion of the femoral vein.

The acknowledged failure of heparin to act on the preformed *in vitro* clot is readily demonstrable.[30] However, the preformed *in vivo* clot has on occasion been seen to disappear. This startling contrast between *in vivo* and *in vitro* action has stimulated us to determine, if possible, the precise action of heparin in the living organism. For this study a method of experimental induction of thrombosis in the rabbit was devised which fulfilled all the requirements and which was uniformly successful.[4]

It has been possible to determine experimentally in animals at what stage of clot

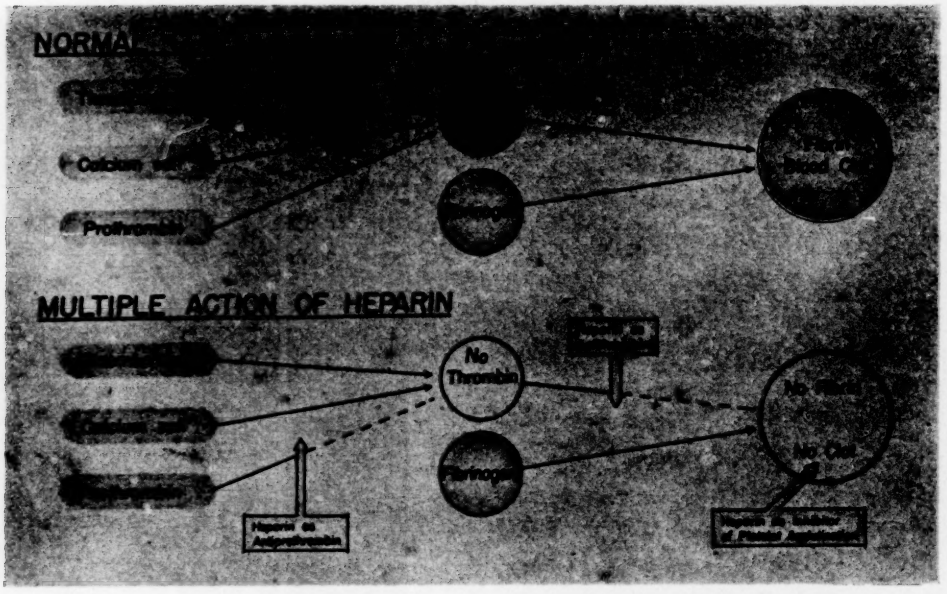


FIG. 2. Graph portraying the mechanism of anticoagulant action of heparin.

formation heparin administration results in solution of the clot and what effect heparin has on the organizing clot.[5,7] In all of the experimental animals heparinization was accomplished by the subcutaneous administration of heparin/Pitkin menstruum, the treatment program being conducted in a manner comparable to that in humans.

Briefly, studies on the effect of heparin in experimental venous thrombosis in the rabbit have yielded the following data:

(1) Red cell clots not organized and containing a minute amount of fibrin (sludge stage) disappear completely under heparin therapy. (Figs. 3 to 8.)

(2) Heparin therapy maintains patent adjacent collaterals and tributaries which ordinarily would become involved in the thrombotic occlusive process. These compensatory collaterals often become as large as the originally occluded vessel. This phenomenon has not been observed in control animals. (Figs. 9, 10 and 11.) It may be assumed, although not necessarily proved, that these processes also occur in obstructed lymphatics.

In a more detailed analysis of these experimental studies[7] several facts were immediately apparent. Patency can be reestablished in experimental veins even as long as six days after a clinically visible and microscopically demonstrable thrombus is present. Since it is well known that heparin *in vitro* has no effect on fibrin, it seems difficult to explain the dissolution of clots up to and including the sixth day after thrombus formation. A critical review of the physical changes resulting in clot formation may afford a possible explanation of our results. The classical early red cell clot consists of red cells enmeshed in an interlacing fibrin network. After varying periods of time, organization occurs within the clot wherein the red cells and fibrin are replaced by young fibrous connective tissue.

In the light of recent work on the functional pathology of experimental frostbite[12,13] and on the blood flow in malaria and in traumatic shock,[25] it may be inferred that the natural history of the classical clot as generally described is not complete. In the presence of injury or infectious disease, Knisely and his co-workers have observed that red cells become "sticky" and adhere to one another; at first, in small clumps which soon become progressively

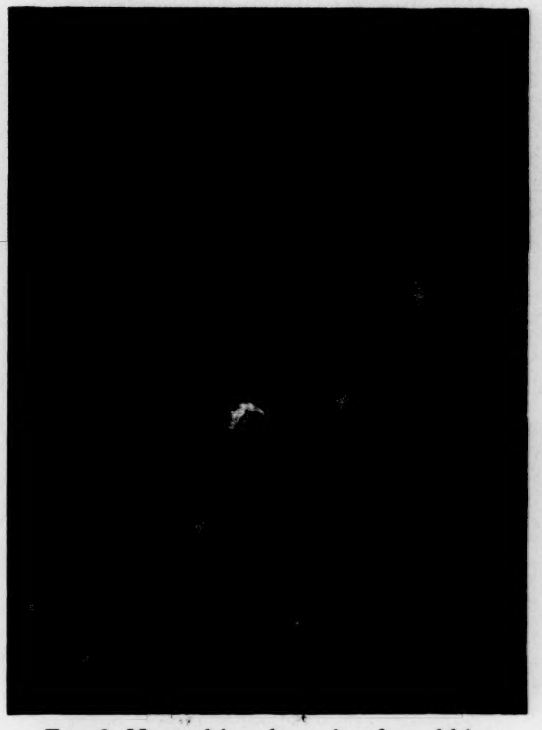
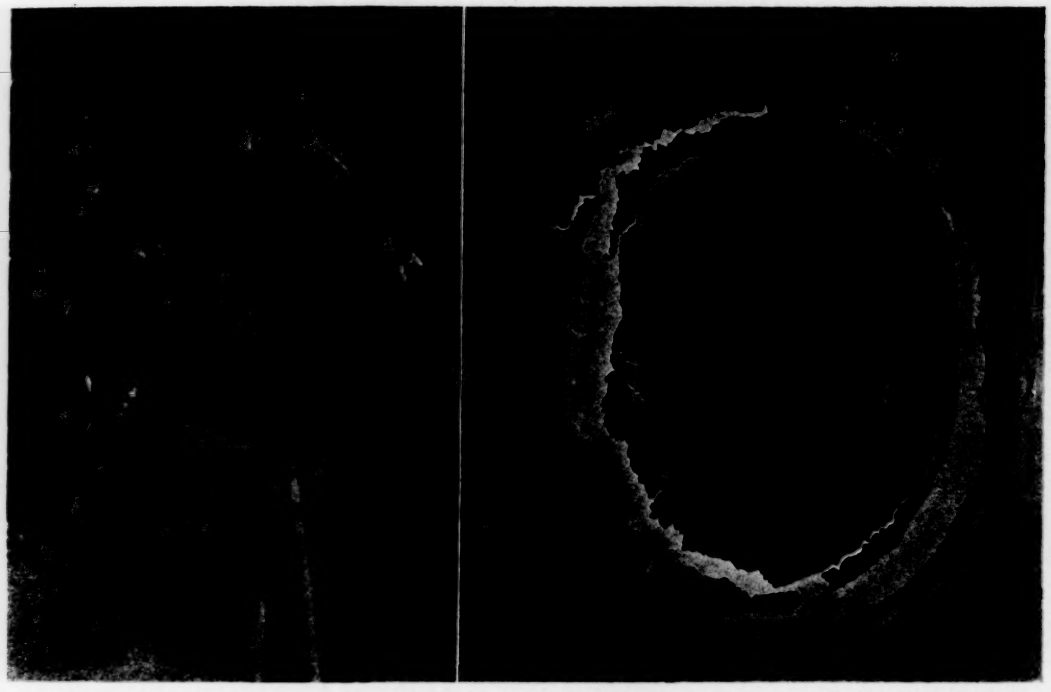


FIG. 3. Normal jugular vein of a rabbit.

FIG. 4. Photomicrograph of normal jugular vein of a rabbit, all coats intact; × 43.

larger so that blood flow rapidly slows down and the blood itself appears as a thick mucky sludge, similar to the sludge phenomenon in experimental frostbite. The mechanism whereby the red cells become sticky is mediated through the formation of a thick, glassy, cottony precipitate whose appearance and consistency suggests that it might be fibrin or a fibrin-like material. It thus follows that the earliest stage of clot formation, as portrayed in our experimental investigation, may well be represented by a large mass of red cells agglutinated to one another and not as yet exhibiting the usual interlacing fibrin network. In the progressive growth of a clot sludge formation is ever present, both as the propagating tail and as part of the unorganized body of the clot. It is significant that in every instance when pure sludge formation was noted microscopically, despite clinically palpable clot formation, the clot disappeared completely under heparin therapy.

The extent and apparently the speed of recanalization of experimental thrombi is enhanced by the use of heparin. When the vein is so grossly occluded as to preclude the resumption of clinical patency, recanalization is still greater in degree and extent under heparin therapy. In the presence of occluded veins which cause definite obstruction to circulation, the opening of adjacent collateral venous channels is so extensive in the presence of heparin that the combined cross sectional area of the collateral system appears as great, if not greater than that of the original veins. Any attempt to explain the apparent dissolution of the frank fibrin clot and the rapid recanalization of the late clot under heparin influence must necessarily be speculative. Studies are in progress in an effort to clarify these moot points. Conceivably, a contributing factor in stimulating reparative processes of the mature fibrin clot, such as organization and recanalization, is the demonstrable effectiveness of heparin in enhancing and maintaining an elaborate collateral circulation. It is generally conceded that the phenomenon of recanalization



5 6

FIG. 5. Non-heparinized control; jugular veins of a rabbit six days after ligation and hammering; visible and palpable clots have been induced.

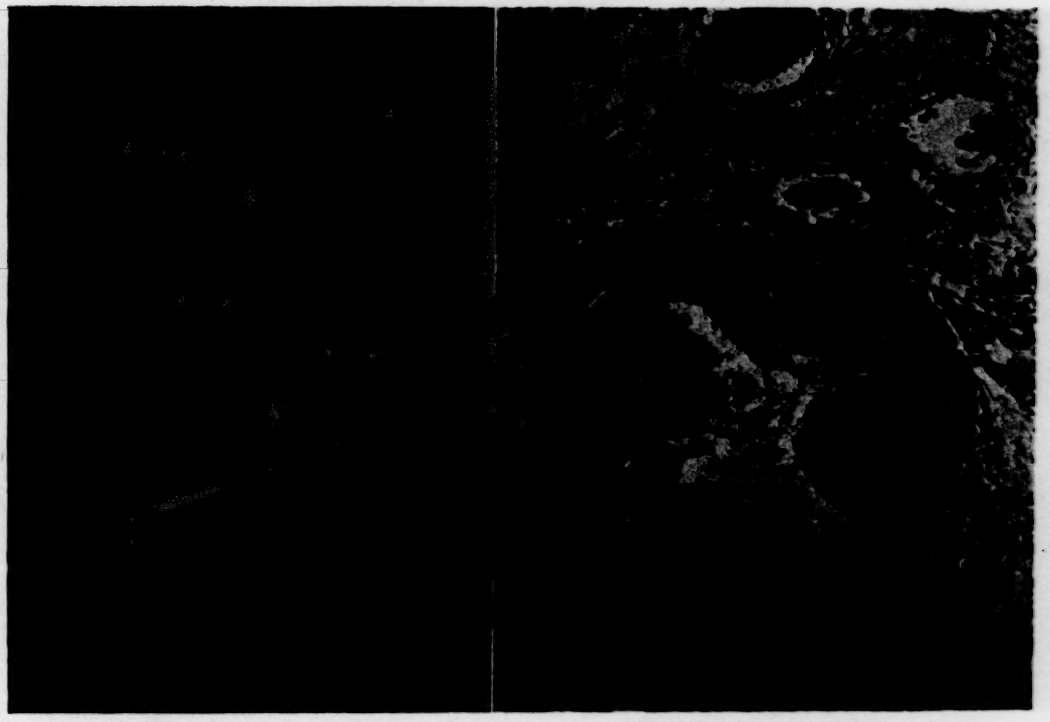
FIG. 6. Photomicrograph of jugular vein (Fig. 5) with all coats intact. There is no classic evidence of clot, the blood being present as particulate masses with a minimum of fibrin (sludge); × 30.

is to a large extent predicated on physical factors. It is evident that the larger column of fluid blood, resulting from heparinization, pounding against small, recanalizing channels may well be responsible for accelerating and augmenting organization and recanalization.

Treatment. Although methods of treatment of thrombophlebitis and/or phlebothrombosis are legion, two major thoughts have dominated the clinical scene during the past five years, namely, vein ligation and anticoagulation therapy.

Surgical Interruption of Veins. While our contrary views on the matter of vein ligation have been set forth elsewhere[3] the literature abounds in articles advocating this form of therapy. The surgical approach to the problem of thromboembolism was initiated in America by Homans[17] and later elaborated by Welch and Faxon,[31] Fine,[32] Allen and his associates,[33] deTakats[34] and others. The knowledge that the majority of such emboli stem from the veins of the lower extremities led these investigators to divide the suspected vein, after preliminary thrombectomy, on the faintest suspicion of phlebothrombosis. Indications for vein ligation have been based for the most part on clinical signs, whether or not corroborated by positive phlebograms.[21,35]

In the few years during which unilateral superficial femoral vein ligation has been practiced, it has become apparent that fatal pulmonary emboli may derive from an unsuspected thrombotic process on the contralateral side so that bilateral superficial vein interruption has now become common practice. Even this procedure does not offer absolute protection against embolization. Allen, Linton and Donaldson report six deaths due to emboli subsequent to femoral vein ligation in a series of 1,300 patients.[36] There are, furthermore, known fatalities in



7 8

FIG. 7. Jugular veins of a rabbit six days after ligation and hammering, with fourteen days of heparinization superadded. The walls are thickened but no gross evidence of thrombosis is apparent. Compare with Figures 3 and 5.

FIG. 8. Photomicrograph of jugular vein (Fig. 7) with all coats intact; no evidence of clot or fibrin; note beginning collateralization. Compare with Figure 6.

which the offending embolus originated from the profunda femoris vein proximal to the site of ligation of the superficial femoral vein. This has prompted Linton[21] to divide the common femoral vein. The resultant edema from this procedure has admittedly been troublesome and has been observed to persist for a year or two or longer. Since embolization from the profunda femoris may occur, Homans[37] has been impelled to advocate common iliac and even inferior vena cava ligation. However, Homans reports that technical difficulties militate against thrombectomy, particularly in a phlebothrombosis of long standing, so that ligation must of necessity be carried out in continuity, even if a clot is present proximal to the ligature. Obviously embolization from the proximal thrombus is not beyond the realm of possibility.

It must be stated that, although the majority of emboli derive from the peripheral veins, the initiating site may at times be the pelvic veins for which surgical intervention, if it is to be effective, must perforce be a formidable procedure. Finally, in those patients with long standing thrombophlebitis, phlegmasia alba dolens, in which multiple infarcts have occurred, any surgical intervention short of vena cava ligation offers little prospect of cure.

It thus appears that the pendulum of surgical therapy has reached the peak of its swing and the relatively innocuous procedures of a few years ago are being supplanted by operations of considerable magnitude. In view of the failure to achieve a complete thrombectomy consistently in patients in whom adherent clot was found far proximal to the phlebotomy or because of the hazard of subsequent postoperative

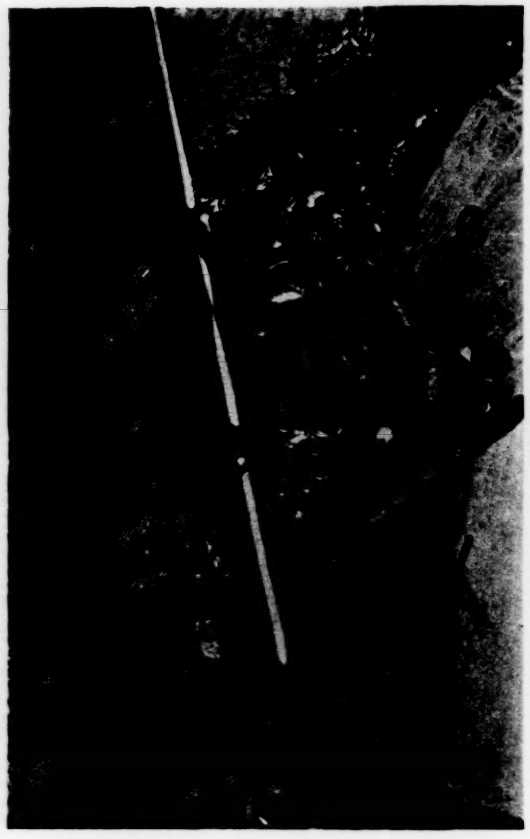


FIG. 9. Jugular vein of a rabbit fourteen days after ligation and hammering with fourteen days of heparinization superadded. Minimal, if any, blood flow through the traumatized vessel (v). Note the rich, dilated, extensive compensatory collaterals (c). Compare with control, non-heparinized veins in Figure 11.

FIG. 10. Collateral vessel fourteen days after ligation and hammering of jugular vein with fourteen days of heparinization superadded. All the characteristics of a normal vein are present; × 27.

embolizations, whether or not they are sublethal, Bancroft[9] has advocated the postoperative use of heparin. Indeed, Allen[21] reports that for patients with multiple infarcts heparinization has been used with definite benefit.

Although saving of life is the prime consideration of surgery, the resultant edema is most troublesome to the patient. Operative procedures which interrupt not only venous but also lymphatic channels contribute considerably to this edema. While conservative treatment without heparin, consisting in the main only of bed rest and sedation, may occasion considerable edema in those who survive, the supplemental use of heparin/Pitkin menstruum results in minimal residual edema, certainly far less than that observed following operative intervention.

It appears that the surgical approach, while efficacious in the majority of cases, has its limitations. In view of the complications of the surgical approach in the treatment of thromboembolic disease, it is apparent that the anticoagulants assume prime importance.

Anticoagulation Therapy. Anticoagulation therapy deals with the abnormal physiology of blood and lymph in the body. Of the anticoagulants, dicumarol and heparin have been the most widely used.

Recourse to dicumarol is understandable because it can be administered orally. The effectiveness of the drug, however, is tempered by the difficulty in planning dosage

schedules and more important, because of its dangerous complications.[38–42] There is great variability in the response to dicumarol, this lack of uniformity of response being present even in the same individual. Fixed dosage schedules cannot be established; patients must be individualized. The action of dicumarol is slow, from forty-eight to seventy-two hours being required before its therapeutic effectiveness is achieved. This delay in action is due to the fact that dicumarol's anticoagulation action is a reflection of its attack on the liver, inhibiting the formation of prothrombin.

Due to delay in action and the variability of the patient's response the drug is not always useful in the early critical stages of coronary thrombosis, in arterial thromboembolism generally and in arteriotomy or major pulmonary embolism when prompt anticoagulation effect is imperative. The delayed action and prolongation of effect after cessation of therapy are disadvantages during or shortly after operative procedures as well as in patients with anticipated, threatened or actual hemorrhage. Instances have been observed in which embolism, thromboses or progression of existing venous thromboses have occurred despite low blood prothrombins induced by dicumarol.[40] Patients receiving dicumarol require daily prothrombin determinations. Dicumarol should not be employed unless there are proper laboratory facilities for prothrombin determinations by acceptable technics. The latter are time consuming and relatively expensive.

In the presence of liver disease the use of dicumarol is contraindicated. It has been attended by irreversible hemorrhage and death.[41] Transfusions of fresh blood alone do not arrest the hemorrhagic tendency occasioned by the drug. Massive dosages of vitamin K are required which may, in turn, reinduce thrombosis.[42]

In summary then, the delayed action, potential hazards, the unpredictable treatment failures and the requisite complicated but indispensable laboratory procedures militate against dicumarol as the anticoagulant of choice.

FIG. 11. Non-heparinized control; jugular veins of a rabbit fourteen days after ligation and hammering. The veins are thickened and fibrotic. Note the absence of compensatory collaterals. Compare with Figure 9.

The properties of heparin which render it uniquely applicable in thromboembolic disease have already been enumerated. Until recently the routine use of heparin has been limited by the expense, the huge amount of drug required in the individual case and the cumbersome method of administration, which requires a continuous venoclysis or repeated daily intravenous dosage. The restriction of motion of the patient, the almost absolute certainty that superficial angiitis would eventually occur at the site of injection and the haphazard control of the clotting time rendered heparin therapy useless unless constant supervision was available.

In an attempt to achieve prolonged absorption of heparin, pellet and capsule

implantation in experimental animals was attempted. Erratic, unpredictable effects were observed. However, a slower and more uniform distribution of heparin was obtained by incorporation of the drug in the Pitkin menstruum developed to regulate the rate of release of water-soluble drugs injected intramuscularly or subcutaneously.[1,2]

TABLE I
HEPARIN/PITKIN MENSTRUUM FORMULAS

	With Vasoconstrictors		Without Vasoconstrictors	
Heparin, sodium salt, mg.	300.0	200.0	300.0	200.0
Epinephrine hydrochloride, mg.	1.0	1.0	0	0
Ephedrine sulfate, mg.	25.0	25.0	0	0
Chlorobutanol, mg.	0.5	0.5	0.5	0.5
Eucupin dihydrochloride, mg.	1.0	1.0	1.0	1.0
Pitkin menstruum, cc.	3.0	2.0	3.0	2.0

The ingredients of the Pitkin menstruum are gelatin 15 to 30 per cent, dextrose 5 to 12 per cent, glacial acetic acid 0.5 per cent and sufficient distilled water to make 100 per cent. The rate of liberation of the contained heparin is inversely proportional to the viscosity of the menstruum; the optimum percentage of gelatin and dextrose were found to be 18 and 8 per cent, respectively, for the preparation containing heparin.

Heparin/Pitkin Menstruum. The ampuls* for clinical use (Table 1) are as follows:

Heparin/Pitkin menstruum (v.c.)

Ampuls, 2 cc.—each ampul containing 200 mg. heparin sodium salt with vasoconstrictors.

Ampuls, 3 cc.—each ampul containing 300 mg. heparin sodium salt with vasoconstrictors.

Heparin/Pitkin menstruum (plain)

Ampuls, 2 cc.—each ampul containing 200 mg. heparin sodium salt; no vasoconstrictors.

Ampuls, 3 cc.—each ampul containing 300 mg. heparin sodium salt; no vasoconstrictors.

Dosage Plan. In general, body weight and individual reactivity dictate the amount of heparin/Pitkin menstruum to be used in a given case. For the initial injection, body weight may be used as a guide. Patients weighing up to approximately 150 pounds (67.8 Kg.) should be given an initial dose of 300 mg. of heparin sodium salt, patients over this weight should be given an initial dose of 400 mg. Subsequently, the dosage should be adjusted according to the intensity of the "heparin effect" as estimated by the coagulation time. Compared with a normal coagulation time of nine to fifteen minutes (Lee-White modification of Howell's method), a coagulation time of thirty to sixty minutes is considered an adequate "heparin effect." In actual practice it will be found that a conventional dose of 300 mg. of heparin will suffice for about 90 per cent of subjects who are normal reactors. The remaining 10 per cent are either hyper- or hyporeactors requiring 200 or 400 mg. dosages, respectively.

Method of Administration. (1) Warm the ampul gently either by holding it under running, hot tap water or immersing it in a container of hot tap water until the contents become fluid; (2) shake thoroughly to disperse any precipitated material; (3) draw the contents of the ampul into a dry, sterile 5 or 10 cc. syringe, using a sterile needle, gauge 18 (2 inch length). After the contents have been drawn up, the 18-gauge needle should be replaced by a 20-gauge needle for the actual injection; (4) inject the contents immediately into the deep subcutaneous (or superficial intramuscular) tissue, preferably in the anterior or lateral aspect of the thigh. When subsequent injections are required, use the right and left thighs alternately and avoid sites of previous injection. Do not inject into sites where pressure may be exerted upon the injection area; (5) be certain that the contents of the syringe are not too hot prior to the injection. The syringe and contents should feel only slightly warm and (6) do not apply either heat or cold to areas of deposition unless for

* Prepared and distributed by William R. Warner & Co., Inc., New York.

purposes of accelerating or retarding release of the drug.

Clinical Use. In the average patient use the entire contents of one 3 cc. ampul containing 300 mg. of heparin sodium salt. This dose should be sufficient to keep the patient "heparinized" for approximately two days. (Fig. 12.) Therefore, administer the contents of one 3 cc. ampul every second day throughout the requisite period of heparinization. If the patient receives a blood transfusion during the period of heparinization, administer the contents of one 3 cc. ampul immediately following the transfusion, irrespective of when or how many previous deposits have been given.

Method of Following the Patient's Clinical Course. The effect of heparin is judged by and based on determination of the blood coagulation time, which should be estimated daily throughout the period of heparinization. The capillary tube method is inaccurate and should not be used. The Lee-White modification of Howell's method for determination of blood coagulation time is recommended. The technic of performing and estimating coagulation time is as follows:

(1) Place four chemically clean, dry 75 × 10 mm. test tubes in a rack. (2) With a sterile, dry syringe and needle withdraw about 2 cc. of venous blood from the subject. The test is timed from the moment the blood is first observed in the syringe. Remove the needle from the syringe. (3) Gently distribute approximately 0.5 cc. of blood into each test tube. Discard the last air-containing fraction. (4) All glassware, syringes and needles must be absolutely dry. Moisture, alcohol, etc., invalidate the determination. (5) The vein must be negotiated cleanly. If difficulty is encountered, it is best to use a fresh needle and syringe. Even a small amount of tissue juice aspirated into the syringe will give a false result. (6) Once the blood is placed in the test tubes they must be disturbed as little as possible while observing for the end point. It will be noticed that well heparinized blood will sediment very rapidly. The tubes should not be shaken after sedimentation of the blood. Look for clotting in the red cell layer as well as in the plasma

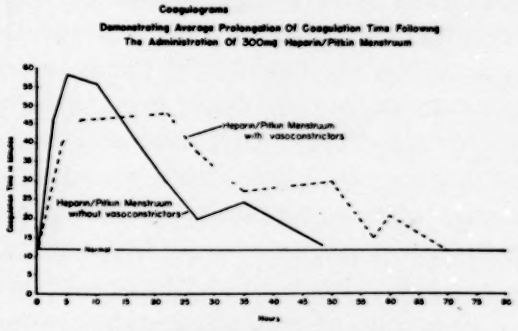


FIG. 12. Coagulograms demonstrating average prolongation of coagulation times following the administration of 300 mg. heparin/Pitkin menstruum.

layer by gently tilting the tubes. In unclotted blood the red cell layer will flow as the tube is angled. (7) First, gently tilt one tube and note the flow of the red cell layer. If the flow is rapid discard the tube and wait about five minutes before the second tube is angled. In this way the end point may be approximated and then finally accurately determined from the third or fourth tube. Once any of the tubes are disturbed they should be discarded, and (8) the patient's coagulation time should be determined before heparinization for control purposes, after which the coagulation time should be estimated daily (twenty-four hours after the heparin injection and immediately before the next injection.

REACTIONS, COMPLICATIONS IN THE USE OF HEPARIN/PITKIN MENSTRUUM

(1) The local pain, swelling and tenderness of the earlier preparations is ascribable to the precipitate which was found to be due to a combination of heparin and eucupin. The pain factor induced by this precipitate was at times excessive but could be con-

trolled by adequate sedation. This objection to the preparation, the pain factor so disturbing to the patient, has now been controlled by careful buffering so that the pH of the gel is more physiologically acceptable and the tendency to precipitation noted in the original ampuls is overcome. Other side effects of the heparin Pitkin menstruum preparations are trivial.[3,5,10] On rare occasions some oozing will occur from the needle puncture. In the several thousand deposits that have been made there was but one instance of hematoma of sufficient proportion to justify interruption of heparinization in a patient with postpartum thrombophlebitis. The patient made an uneventful recovery.

(2) Following the administration of a dose of 200 or 300 mg. of heparin sodium salt combined with vasoconstrictor drugs, the patient will occasionally complain of palpitation and nervousness. These reactions require no treatment and disappear within a short time.

(3) Digitalis is said to inhibit the anticoagulant action of heparin. If possible avoid the use of this drug during the period of heparinization.

(4) If suspension of heparin activity is desired, small transfusions of whole blood or relatively fresh bank blood will inactivate any circulating heparin. An ice bag applied to the site of deposit or a tourniquet above it will suspend or slow up the absorption of the drug. In our experience the use of protamine for abrupt interruption of heparinization has not been necessary.

(5) In hypertensive patients or those with myocardial disease it is preferable although not mandatory to use heparin without vasoconstrictor drugs in order to avoid the transitory subjective vasoconstrictor effects.

Suggestions for Treatment. (1) In patients with thrombophlebitis it is advisable to inject the heparin into the thigh which is normal. Avoid using the affected thigh for deposition of heparin until the swelling has partially receded. (2) For hyper-reactors employ the 2 cc. ampul which contains 200 mg. of heparin sodium salt. For hyporeactors administer 400 mg. This is accomplished by combining two cc. ampuls each containing 200 mg. of heparin sodium salt. When vasoconstrictors are indicated use only one ampul with vasoconstrictors in the combination, inasmuch as the amount of vasoconstrictor drugs contained in the one ampul will suffice for the entire dose of heparin. (3) As a general rule, for effective heparinization the blood coagulation time should be not less than three times the control coagulation time, i.e., thirty to forty-five minutes as contrasted with a control time of nine to fifteen minutes.

CLINICAL DIAGNOSIS

For optimum results heparin therapy should be inaugurated as early as possible. The advantages of preventing spread of thrombosis before it may give rise to pulmonary embolism or serious local damage are obvious and have been stressed repeatedly in the literature.[43] Admittedly, thromboembolism may be a treacherous and unpredictable condition; at times it occurs catastrophically and without warning. Nevertheless, if one is alert for slight premonitory signs, these will be discovered more often than has been supposed. One such diagnostic sign, described by Allen,[21] is an inexplicable rise in the pulse, temperature and respiration at the same reading or observation. When after operation these have shown the normal downward course, any fresh rise, however small, after the fourth or fifth day must always evoke suspicion. This applies also to the parturient and to patients with fractures. Another sign sometimes observed is an unaccountable feeling of disquietude and restlessness which affects the patient. He may state, perhaps not until questioned, that he was

kept awake during the night by a faint ache and a feeling of cramp in one of the calves, so-called "charley horse," a symptom which may already have disappeared. Complaint of even a slight stitch or pain in the chest must arouse strong suspicion of pulmonary infarction which is confirmed if the patient develops an irritative cough or expectorates blood-streaked sputum. It may be assumed that the majority of so-called "lung complications" observed postoperatively or postpartum, as well as in aged people confined to bed for reasons other than general debility, are due to pulmonary infarcts secondary to thrombosis somewhere in the peripheral parts of the body.

If any of these general signs are noted, a detailed physical examination must be made to elicit the cause. Examination consists of palpation of the groins, inner aspect of the thighs, popliteal spaces, the calves and the veins of the feet for swelling and tender areas. Conspicuous signs need not necessarily be present. In early cases one may note only slight swelling of the lower leg, an increased glossiness and tension of the skin, a faintly cyanotic discoloration in comparison with the other leg and prominence of the superficial veins of one leg as compared with the other. All these signs need not necessarily be present but if one or more of them is observed the probability of an incipient thrombosis is considerably increased.

The most important sign is direct tenderness in the calf, discovered by pressure with the palpating fingers. Such tenderness will be more significant if none is elicited when the muscles of the same level are compressed from side to side. An increase in the consistency of the muscular part of the calf is another customary feature of thrombosis. Finally, the foot is brought into dorsal flexion and if pain is induced (Homans' sign) it is very suggestive of deep venous thrombosis.

Phlebography. The clinical importance of phlebography of the lower extremities is still unsettled. It seemed to us that the latter could be more clearly defined as an aid to the evaluation of the procedure. In a study by Epstein, Wasch and Loewe,[44] apparently normal individuals were subjected to phlebography of the lower extremities, as a result of which the following conclusions seemed warranted. Within its limitations phlebography may provide information as to the patency of the superficial and deep venous circulation. The normal variations which may be observed in phlebograms of the leg make it hazardous to venture a diagnosis in the absence of very striking changes. There is a marked variation in the appearance of the deep leg veins which makes it extremely difficult to reach any trustworthy conclusion as to the presence of intrinsic thrombotic changes in those areas. The appearance of the popliteal and femoral vein is more consistent but here, too, normal variations occur which may confuse the unwary into venturing a diagnosis of thrombotic changes. Because of the difficulty of establishing the normal standard we have abandoned the routine clinical use of phlebography.

ANALYSIS OF RESULTS AND CLINICAL OBSERVATIONS

The clinical deportment of heparin/Pitkin menstruum has been observed in 251 patients representing all forms of venous thromboembolic disease. (Table II.) Some of the categories have afforded more cases than others but, on the whole, there are a sufficient number of cases for purposes of observing and evaluating the effects of heparin/Pitkin menstruum in thromboembolic disease. The results have been most gratifying, being signally successful in thrombophlebitis irrespective of etiology.

The final judgment in any treatment program for thromboembolic disease is predicated on the statistics with respect to pul-

monary embolization. It is noteworthy that of the 251 patients, ninety-five had from one to six pulmonary embolizations prior to initiating subcutaneous heparin therapy. There were five fatalities in this series of 251 patients (1.9 per cent). Four of the fatalities

TABLE II

HEPARIN/PITKIN MENSTRUUM IN THE TREATMENT OF 251 CONSECUTIVE PATIENTS WITH VENOUS THROMBOEMBOLIC DISEASE

Classification	No. of Patients	No. of Patients with Pulmonary Embolization	Deaths Due to Pulmonary Embolization
Post-operative Thrombophlebitis and/or Phlebothrombosis	102	45	3
Thrombophlebitis and/or Phlebothrombosis, Miscellaneous*	92	38	1
Post-partum Thrombophlebitis	30	7	0
Post-infectious Thrombophlebitis	10	0	0
Post-traumatic Thrombophlebitis	8	5	1
Migrating Thrombophlebitis	9	0	0
Totals	251	95	5 (1.9%)**

* Occurring without ascertainable exciting cause (thrombophilia), or as a complication of carcinoma, varicose veins, etc.

** 4 of the 5 treatment failures occurred before the optimum treatment program was established.

came early in our experience and served as an object lesson for standardizing and formulating our present program of therapy and dosage schedules.

The fifth treatment failure occurred in a sixty-three year old obese, white woman who had, at the outset, an obscure clinical syndrome which ultimately proved to be bilateral massive thrombophlebitis with repeated extensive pulmonary embolic episodes. The clinical diagnosis was at no time characteristic and even after thrombotic involvement of peripheral veins was evident, it was believed that the clinical picture was secondary to an underlying malignancy. Heparin/Pitkin menstruum therapy was inaugurated more than three weeks after the known onset of the condition. A standard dosage schedule was administered, the patient receiving 300 mg. of heparin/Pitkin menstruum subcutaneously every other day for five injections with seemingly satisfactory anticoagulation responses. Despite this the patient went into deep shock as a result of massive pulmonary embolus. At necropsy the deep veins of both lower extremities were found to be completely occluded, with massive thromboses extending up to and involving both femorals, iliacs, the inferior vena cava, ovarian veins and renal veins. The extent of the thrombotic lesion, which was never suspected clinically, evidently made the patient refractory to the average doses of heparin. Our experience leads us to believe that there is a parallelism between thrombus mass and heparin requirements. Had the extent of the lesion been recognized and the dosages intensified, further thrombus formation might perhaps have been prevented. It seems hardly likely that the patient would have survived high vena cava ligation, nor is it possible to assume that further embolization would have been obviated. As a result of the experience in this patient the following program has been formulated. Once the diagnosis of thrombophlebitis or venous thromboembolism has been entertained in an individual who has been ill for some time, it must be assumed that the condition has, from the very outset, been one of intravascular thrombosis and a greatly intensified dosage schedule must be instituted. Such a dosage schedule might well be 400 to 500 mg. every other day, or even daily, in order to maintain coagulation times between one and two hours. This compares with a coagulogram of thirty to sixty minutes obtained with conventional dosages of 300 mg. every other day, which is adequate for the average patient. It may well be that patients with massive, widespread thromboses can be salvaged only in this manner, if at all. The importance of early diagnosis in order to obtain optimum results cannot be overemphasized.

In contrast to these treatment failures, mention may be made of seven patients with multiple pulmonary emboli despite vein ligation, with complete recovery following use of the subcutaneous heparin preparation.

Particularly significant and informative are the twenty-two patients who were successfully treated with heparin in the Pitkin

menstruum following single or multiple massive pulmonary embolizations without any manifestation of peripheral vein involvement; these patients could not conceivably be subjects for proximal vein ligation. Finally, it is worthy of comment that in seven patients subcutaneous heparin was successfully employed following failure with dicumarol.

In uncomplicated phlebothrombosis, heparinization need be continued only for seven to ten days, while cases complicated by pulmonary infarction, either single or multiple, require an additional seven to ten days of heparinization. The full heparin effect must be present when the patient is first allowed out of bed and continued until the patient is fully ambulatory. This conservative span of treatment is postulated not only on the basis of clinical experience but also as the result of experimental work indicating the time needed for restoration of the vascular stream and the importance of giving sufficient treatment to allow and promote collateralization and development of the tributary vein system.

It is evident from a critical review of our series of patients that our extensive trial of subcutaneous heparin in the Pitkin menstruum has given good results. Sulfonamides and penicillin may be used in conjunction with heparin but heparin alone in clinically established thrombophlebitis, irrespective of etiology, consistently gives good if not dramatic results. These include diminution of temperature, pain and swelling, which often become manifest within a few hours after initiation of therapy. This improvement is predicated on limitation in the progress of the formed thrombus, while the original inflammation expends itself and the thrombus either resolves or becomes organized. Since there is no further actual propagation of thrombus, there is a rapid and marked diminution in vasospasm. Morbidity is lessened and convalescence accelerated.

Coincident with the institution of heparin therapy the liberal use of papaverine is recommended, 1 to 3 grains every four hours intramuscularly or even intravenously and, later, maintenance dosages by mouth. Smoking is strictly prohibited. Paravertebral block, although used extensively in arterial occlusions, is not used by us in thrombophlebitis as a routine measure since we have found that venous spasm disappears promptly following administration of subcutaneous heparin.

As has been described earlier the general systemic anticoagulation effect of heparin seems to us to be a more rational therapeutic weapon than local vein ligation, especially since the precipitating cause of thrombosis is not yet known and the initiating site of thrombosis can be ascertained in many cases only by vague and indeterminate clinical signs. The ready availability of immediate, adequate and rational conservative treatment without moving the patient has caused vein ligation to be supplanted in our clinic by subcutaneous heparin therapy.

HEPARIN/PITKIN MENSTRUUM IN THE TREATMENT OF THROMBOEMBOLIC DISEASE COMPLICATING THE PUERPERIUM AND GYNECOLOGIC SURGERY

Of the 251 patients with venous thromboembolic disease (Table II) receiving heparin/Pitkin menstruum, fifty-three (Table III) were obstetric or gynecologic patients. Thirty-four of these fifty-three patients were obstetric and nineteen presented gynecologic problems. One of the thirty-four parturients received the treatment for phlegmasia alba dolens which developed forty-eight hours prior to the onset of labor. In the latter patient the therapy was interrupted during actual labor and was begun again in the postpartum period. Instructions to interrupt heparinization at the very onset

of labor were not carried out until several hours after delivery. Significantly in this case there was somewhat less than the anticipated amount of immediate post-delivery bleeding, despite the fact that the patient was actively heparinized at the time of de-

TABLE III
HEPARIN/PITKIN MENSTRUUM IN THE TREATMENT OF 53 PATIENTS WITH THROMBOEMBOLIC DISEASE COMPLICATING THE PUERPERIUM AND GYNECOLOGIC SURGERY

Classification	No. of Patients	No. of Patients with Pulmonary Embolization	Deaths Due to Pulmonary Embolization
Pre-partum Thrombophlebitis	1	0	0
Post-partum Thrombophlebitis	29	7	0
Post-operative Thrombophlebitis and/or Phlebothrombosis			
Cesarean Section	4	1	1
Hysterectomy	15	9	0
Vaginal Plastic	4	1	0
Totals	53	18	1 (5.5 %)

livery. Of the remaining thirty-three parturients, twenty-hine were delivered vaginally and four by cesarean section. Eight of the parturients embolized prior to therapy, in two cases despite femoral vein ligation. Two patients were dicumarol failures prior to inaugurating subcutaneous heparin/Pitkin menstruum therapy. Manifestations of thromboembolism were present in nineteen postoperative gynecologic patients; fifteen following abdominal hysterectomy and four following vaginal plastic procedures. Ten in the group had one or more pulmonary emboli prior to heparin therapy and four patients had emboli despite vein ligations.

The heparin treatment program was that adopted for venous thromboembolism. The span of treatment for uncomplicated thrombophlebitis and/or phlebothrombosis was ten days to two weeks. For patients with pulmonary embolization an additional week or two of therapy was required depending upon the extent of pulmonary infarction. In any event the full heparin effect was present when the patient was first allowed out of bed.

Most informative are the statistics with respect to the patients who had pulmonary embolization. There were eighteen patients in this group with one fatality, representing 1.8 per cent of the entire series of fifty-three patients and 5.5 per cent of the eighteen patients who had suffered from one or more episodes of pulmonary embolization.

The treatment failure, as previously reported, followed sequential femoral vein ligation for recurrent pulmonary embolization incidental to phlebothrombosis following operation for premature separation of the placenta. Subcutaneous heparin was discontinued prematurely two days after the initial left femoral ligation, because the pulmonary findings were attributed to virus pneumonia which was prevalent at the time. The right femoral vein was ligated about ten days after the left femoral vein ligation. Lethal massive pulmonary embolization ensued on the third day following the right femoral vein ligation. Necropsy disclosed old, adherent thrombi in the left iliac and left hypogastric veins which were probably the source of the emboli found occluding the right pulmonary artery and main branch of the left lower lobe.

This fatality, the only one in this group of gynecologic and obstetric patients, must be catalogued as a treatment failure for combined thrombectomy, vein ligation and supplemental subcutaneous heparin therapy, although the latter was suspended after much too short a span of treatment.

One of the obstetric patients suffered a hematoma at the site of one of the injections which did not interfere with the progress of the treatment program, the patient making an uneventful recovery. In this patient, as in all the other patients treated in the early stages of the disease, the hospital stay was definitely curtailed and the disfigurement eliminated or significantly reduced.

While the addition of antibiotics and/or sulfonamides to the treatment program is not discouraged, these are not necessary in the management of the usual type of thromboembolism encountered in obstetric and gynecologic practice. However, should there

be any identifiable infective etiologic condition, an antibiotic and/or chemotherapeutic program should be pursued intensively according to the nature of the infective organism. The mere presence of a febrile reaction does not connote bacterial invasion and may well be attributable to the presence of intravascular thrombosis, particularly when the blood clot engages the vessel wall and precipitates an inflammatory intimal reaction.

The results in this series are satisfactory as judged by effective control of pulmonary embolization, marked amelioration of pain and discomfort, rapid recession of edema, reduction in morbidity, acceleration in convalescence and virtual absence of residual edema particularly when patients are treated without delay.

PROPHYLAXIS

The problem of prophylaxis in the field of thromboembolism has engaged our attention as it pertains to the use of subcutaneous hep rin/Pitkin menstruum.

Despite early ambulation in the postoperative and postpartum patient, there is an irreducible occurrence of venous thromboembolism.[36,45] The widespread general use of anticoagulation therapy in the prospective surgical and obstetric patient, while ideal, is not practical or feasible at present. As a result we have expended a great deal of time and effort in an endeavor to detect the potential clotter, the thrombophiliac. A straw in the wind is the report by Morrison, Richter and Loewe on blood platelet clustering.[46] The report deals with the method and interpretation of a proposed clustering test. Clustering and/or increase in numbers of platelets is directly proportional to their coagulability. The most obvious characteristic of the blood platelet is its clustering propensity.[26,27] A simple routine blood platelet clustering test was devised as a means of establishing the coagulative status of individuals in comparative health and in disease. In a study of 200 subjects a correlation between this test and thromboembolism was indicated. Its value as a means of detecting the clusterer, the thrombophiliac and potential clotter, was suggested. The presumptive thrombophiliac and potential clotter, identified by his blood smear, may then conceivably be protected by proper anticoagulation measures during pregnancy and infections, prior to anesthesia and pre- and postoperatively. Clinical and experimental investigation of the rôle of blood platelet clustering in health and disease is being pursued.

While the use of anticoagulants preoperatively is not generally advocated at present, its prepartum use has been suggested in recent reports.[47,48] Our own related experience with heparin/Pitkin menstruum in the obstetric wards may well suggest its ultimate adoption as a prophylactic prepartum measure.

A rich field for prophylaxis is in the management of patients with severe coronary artery disease and coronary artery incompetency who are extremely suceptible subjects for coronary artery thrombosis. This was originally suggested by the ease with which heparinization was continued and accomplished for long periods of time in ambulatory patients who were up and about following severe intravascular thromboses. We consistently encountered patients who required doses of 300 to 400 mg. of heparin in the Pitkin menstruum every other day in order to achieve adequate coagulograms during the active phases of the disease. These same patients, when there was no longer any clinical or other evidence of the persistence of thrombosis, could then be maintained in a heparinized state on as little as 100 mg. of heparin in the Pitkin menstruum deposited every second to seventh day or longer. This spacing permitted the patients to be treated as ambulatory subjects without inconvenience. As already

indicated there is apparently a direct relationship between the mass and extent of thrombosis and the degree of response to heparin. As the clots disappear the individual becomes less resistant and more responsive to the anticoagulant.

The results of our prophylactic management of ambulatory patients with thrombophilia, recurrent thrombophlebitis, potential coronary artery thrombosis, peripheral vascular disease with menace of complicating thrombosis, or the cardiovalvular patient with or without auricular fibrillation who is suspected of having thrombi in the chambers of the heart or in peripheral veins, have been sufficiently gratifying to justify continuation of the project.

The prophylactic use of heparin/Pitkin menstruum in blood vessel surgery has been recommended by Blakemore and Lord[49] and its use in the prevention of gangrene following frostbite is suggested by the experimental work done in this field.[12,13]

HEPARIN/PITKIN MENSTRUUM IN THE TREATMENT OF ARTERIAL THROMBOTIC DISEASE

Results in the conservative treatment of venous thromboembolic disease with subcutaneous heparin in the Pitkin menstruum have been so gratifying that it seemed logical to apply this therapy to the management of arterial thrombotic disease. Exploratory studies were done in order to observe the clinical behavior of this preparation in the presence of various types of intra-arterial clotting. The clinical observations were sufficiently promising to justify a preliminary report.[6]

Peripheral Vascular Disease. The various arterial lesions included in this study were intra-arterial emboli, diabetic gangrene, thromboangiitis obliterans and ergotism.

Although the pathogenesis differs in the various thrombotic diseases of the peripheral arteries the common denominator is thrombus formation. While recanalization of thrombus may supervene sufficiently to maintain the vascular stream and retain the viability of the affected limb, as a rule loss of tissue with gangrene is the ultimate fate of the untreated case of intra-arterial thrombotic occlusion. Through the use of heparin propagation of thrombus is inhibited and the patency of the affected vessel and uninvolved collaterals is maintained. As a result loss of tissue is minimized or completely obviated and recanalization of the affected major vessel is enhanced. Clinical observations thus far have shown satisfactory response in terms of amelioration of pain, restoration of normal color, tone and lividity to the tissues, delineation of any gangrenous process and increase in pulsation of blood vessels in the affected parts. In general, those patients fared best who received the optimum treatment program within a few hours after the occlusive process became evident.

It is advisable to use heparin without vasoconstrictor drugs (Table 1) in thrombotic arterial disease in order not to aggravate the complicating factor of arterial spasm. This may necessitate more frequent administration or a stepped up dosage plan (400 mg. every other day or daily) because of the more rapid depletion of the individual deposit.

Papaverine is used concomitantly in liberal dosages, first by the intramuscular or intravenous route in 1 to 3 gr. dosages and subsequently by mouth in maintenance dosages of 1 to 1½ gr. every four hours. Paravertebral sympathetic block is used when indicated and repeated whenever necessary in the presence of protracted vasospasm. The vasospasm is apparent for the most part during the early stages of the treatment program before heparinization is in full effect. Rarely is sympathetic block necessary following the first or second deposit of heparin/Pitkin menstruum. The

conjoint use of Etamon (tetraethylammonium)* as a means of supplanting sympathetic nerve block is being explored.[50]

Heparin/Pitkin Menstruum in the Treatment of Thrombosis of Cerebral Arteries or of Retinal Vessels. This has been attempted with signal success only in the few patients treated very soon after the thrombosis occurred. A delay of but a few hours results in irreversible damage to brain tissues due to the ischemia and irreversible damage to the receptor mechanism of the eye. In cerebral thrombosis there is the added hazard of distinguishing between cerebral hemorrhage and cerebral thrombosis; when there is any possible equivocation regarding the diagnosis, anticoagulation therapy must, of course, be withheld.

Heparin/Pitkin Menstruum in Coronary Artery Thrombosis. Coronary artery thrombosis offers a very fertile field for anticoagulation therapy. In coronary artery thrombosis there is a triphasic therapeutic attack. First, and most important perhaps, is to prevent propagation of the thrombus from what, in many instances, is merely an occlusive involvement of small twigs of the coronary vessels. In this manner it is hoped to limit the degree of myocardial infarction and consequent myocardial damage. All too often the propagation thrombus is the lethal factor. The second treatment approach is prevention of embolization from mural thrombi secondary to the myocardial infarction. The third phase of the treatment is leveled at the not infrequent thrombotic involvement of deep venous channels resulting from slowing of the vascular stream in the bedridden convalescent patient. The ominous resultant pulmonary embolization may be clinically confusing at times and erroneously attributed to cardiac factors. Dicumarol is admittedly useful only in the second and third phases of therapy[51–53] and is not helpful, because of its delayed action, in the initial phase of thrombus propagation. Heparin/Pitkin menstruum, because of its prompt action and simplicity of subcutaneous administration, would seem to be the anticoagulant of choice, particularly in the initial and important aspect of coronary thrombosis. The results in a controlled series of patients with acute coronary thrombosis, electrocardiographically confirmed, have thus far been most encouraging. For optimum effects the immediate administration of anticoagulation therapy is essential.

* We wish to thank Parke, Davis & Company for generous supplies of this drug.

SUMMARY AND CONCLUSIONS

1. The functional pathology of intravascular clotting has been outlined as a basis for evaluating the treatment of thromboembolic disease. The rationale of anticoagulation therapy has been presented.

2. Experimental investigations and clinical observations indicate that heparin plays a vital rôle in arresting the progress of intravascular thrombosis and promotes restoration of the vascular stream. It also enhances collateralization.

3. Over 400 patients with various forms of thromboembolic disease have been treated with heparin/Pitkin menstruum. This series included 251 consecutive patients with venous thromboembolic disease.

4. The treatment of venous thromboembolic disease with subcutaneous heparin in the Pitkin menstruum was attended with lessened morbidity, prompt and rapid clinical improvement and little or no residual edema. The causative factors responsible for the five treatment failures have been analyzed. Treatment failures with other methods have subsequently ended in recovery following the routine administration of the heparin/Pitkin menstruum preparation.

5. Exploratory studies in the field of prophylaxis and in the treatment of various arterial thrombotic disorders, including

coronary artery thrombosis and peripheral vascular disease, are sufficiently promising to justify further intensive investigations.

6. As a result of observations of its clinical deportment in over 400 patients with thromboembolic disease, the subcutaneous administration of heparin in the Pitkin menstruum is recommended as a safe, simple, practical and effective method for anticoagulation therapy of intravascular thrombosis.

REFERENCES

1. Loewe, L., Rosenblatt, P. and Lederer, M. A new method of administering heparin. *Proc. Soc. Exper. Biol. & Med.*, 50: 53–55, 1942.
2. Loewe, L. and Rosenblatt, P. A new practical method for subcutaneous administration of heparin: preliminary report. *Am. J. M. Sc.*, 208: 54–63, 1944.
3. Loewe, L., Rosenblatt, P. and Hirsch, E. Venous thromboembolic disease. *J. A. M. A.*, 130: 386–393, 1946.
4. Hirsch, E. and Loewe, L. A method for producing experimental venous thrombosis. *Proc. Soc. Exper. Biol. & Med.*, 63: 569–572, 1946.
5. Loewe, L. and Hirsch, E. Heparin in the treatment of thromboembolic disease. *J. A. M. A.*, 133: 1,263–1,268, 1947.
6. Richter, I. H., Eiber, H. B. and Loewe, L. Subcutaneous heparin in the treatment of arterial thrombotic disease: preliminary report. *Surgery*, (to be published).
7. Loewe, L., Hirsch, E. and Grayzel, D. M. The action of heparin on experimental venous thrombosis. *Surgery*, (to be published).
8. Greene, H. J. and Loewe, L. Heparin/Pitkin menstruum in the treatment of thromboembolic disease complicating the puerperium and gynecological surgery. *Am. J. Obst. & Gynec.* (To be published.)
9. Bancroft, F. W. Proximal ligation and thrombectomy for phlebothrombosis of the femoral and iliac veins. *Ann. Surg.*, 121: 175, 1945.
10. Evans, J. A. and Boller, R. J. The subcutaneous use of heparin in anticoagulation therapy. *J. A. M. A.*, 131: 879–882, 1946.
11. Bancroft, F. W. The surgical treatment of phlebothrombosis in obstetric and gynecologic patients. *Am. J. Obst. & Gynec.*, 53: 109–116, 1947.
12. Lange, K., Boyd, L. J. and Loewe, L. The functional pathology of frostbite and the prevention of gangrene in experimental animals and humans. *Science*, 102: 151–152, 1945.
13. Lange, K. and Loewe, L. Subcutaneous heparin in the Pitkin menstruum for the treatment of experimental human frostbite. *Surg., Gynec. & Obst.*, 82: 256, 1946.
14. Rössle, R. Ueber die Bedeutung und die Entstehung der Wadenvenenthrombosen. *Virchows Arch. f. path. Anat.*, 300: 180, 1937.
15. Neumann, R. Ursprungszentren und Entwicklungsformen der Beinthrombose. *Virchows Arch. f. path. Anat.*, 301: 708, 1938.
16. Frykholm, R. The pathogenesis and mechanical prophylaxis of venous thrombosis. *Surg., Gynec. & Obst.*, 71: 307, 1940.
17. Homans, J. Venous thrombosis in the lower limbs: its relation to pulmonary embolism. *Am. J. Surg.*, 38: 316, 1937.
18. Bauer, G. Venographic study of thromboembolic problems. *Acta chir. Scandinav.*, 84: 1, 1940.
19. Homans, J. Circulatory Diseases of the Extremity. New York, 1939. The Macmillan Company. Varieties of thrombophlebitis of limbs; their origin, course and treatment. *Am. J. Surg.*, 44: 3, 1939.
20. Ochsner, A. Intravenous clotting. *Surgery*, 17: 240, 1945.
21. Allen, A. W., Linton, R. R. and Donaldson, G. A. Venous thrombosis and pulmonary embolism: further experience with thrombectomy and femoral vein interruption. *J. A. M. A.*, 128: 397, 1945.
22. Bauer, G. Heparin in venous thrombosis. *J. A. M. A.*, 131: 196, 1946.
23. Greene, R. Immediate vascular changes in true frostbite. *J. Path. & Bact.*, 55: 259, 1943.
24. Rotnes, P. L. and Kreyberg, L. Eine Methode zum experimentellen Nachweis von Stase mittels spezieller Präparate, *Acta path. et microbiol. Scandinav.*, 11: 162, 1932.
25. Knisely, M. H., Eliot, T. S. and Bloch, E. H. Sludged blood in traumatic shock. *Arch. Surg.*, 51: 220, 1945.
26. MacKay, W. Blood platelet: its clinical significance. *Quart. J. Med.*, 24: 285, 1931.
27. Wright, H. P. Adhesiveness of blood platelets in normal subjects with varying concentrations of anti-coagulants. *J. Path. & Bact.*, 53: 255, 1941. Changes in adhesiveness of blood platelets following parturition and surgical operations. *J. Path. & Bact.*, 54: 461, 1942.
28. Quick, A. J. The Hemorrhagic Diseases and the Physiology of Hemostasis. Springfield, Ill., 1942. Charles C. Thomas, Publisher.
29. Jorpes, J. E. Anticoagulant therapy in thrombosis. *Edinburgh M. J.*, 53: 222, 1946.
30. Rabinovitch, J. and Pines, B. Effect of heparin on experimentally produced venous thrombosis. *Surgery*, 14: 669, 1943.
31 Welch, C. E. and Faxon, H. H. Thrombophlebitis and pulmonary embolism. *J. A. M. A.*, 117: 1,502, 1941.
32. Fine, J., Frank, H. A. and Starr, A. Recent experiences with thrombophlebitis of the lower extremity and pulmonary embolism. *Ann. Surg.*, 116: 574, 1942. Starr, A., Frank, H. A. and Fine, J. The venographic diagnosis of thrombophlebitis of the lower extremities. *J. A. M. A.*, 118: 1,192, 1942.
33. Allen, A., Linton, R. R. and Donaldson, G. A. Thrombosis and embolism: review of 202 patients treated by femoral vein interruption. *Ann. Surg.*, 118: 728, 1943.
34. deTakats, G. Surgical treatment of thromboembolism and its sequelae. *Bull. New York Acad. Med.*, 20: 623, 1944.

35. Ochsner, A. In discussion on Allen, Linton and Donaldson.[21]
36. Allen, A. W., Linton, R. R. and Donaldson, G. A. Venous thrombosis and pulmonary embolism. *J. A. M. A.*, 133: 1,268–1,276, 1947.
37. Homans, J. Quiet venous thrombosis of the lower limbs: preferred levels for interruption of veins; iliac section or ligation. *Surg., Gynec. & Obst.*, 79: 70, 1944.
38. Prandoni, A. and Wright, I. The anticoagulants heparin and the dicoumarin 3,3′ methylene-bis (4-hydroxycoumarin). *Bull. New York Acad. Med.*, 18: 433, 1942.
39. Cahan, A. Hemorrhage and purpura caused by dicoumarin. *New England J. Med.*, 228: 820, 1943.
40. Wasserman, L. R. and Staats, D. Clinical observations on the effect of 3, 3′-methylenebis (4-hydroxycoumarin). *Am. J. M. Sc.*, 206: 466, 1943.
41. Shlevin, E. L. and Lederer, M. Uncontrollable hemorrhage after dicumarol therapy with autopsy findings. *Ann. Int. Med.*, 21: 332, 1944.
42. deTakats, G. and Fowler, E. F. The problem of thromboembolism. *Surgery*, 17: 153, 1945.
43. Bauer, G. Thrombosis, early diagnosis and abortive treatment with heparin. *Lancet*, 1: 447–450, 1946.
44. Epstein, B. S., Wasch, M. G. and Loewe, L. An evaluation of phlebography of the normal lower extremity. *Am. J. Roentgenol.*, (to be published).
45. Blodgett, J. B. and Beattie, E. J. Early postoperative rising: a statistical study of hospital complications. *Surg., Gynec. & Obst.*, 82: 485–489, 1946.
46. Morrison, M., Richter, I. H. and Loewe, L. Blood platelet clustering. (To be published.)
47. Leissner, H. Use of heparin in obstetrical practice, as a means of preventing thrombosis. *Acta med. Scandinav.*, 107: 127, 1941.
48. Barnes, A. C. and Ervin, H. K. The effect of anticoagulants of postpartum bleeding. *Surg., Gynec. & Obst.*, 83: 528, 1946.
49. Blakemore, A. H. and Lord, J. W. A nonsuture method of blood vessel anastomosis. *J. A. M. A.*, 127: 685 and 748–753, 1945.
50. Berry, R. L., Campbell, K. N., Lyons, R. H. Moe, G. J. and Sutler, M. R. The use of tetraethylammonium in peripheral vascular disease and causalgic states. *Surgery*, 20: 525, 1944.
51. Nichol, E. S. and Page, S. W., Jr. Dicumarol therapy in acute coronary thrombosis. *J. Florida M. A.* 32: 365, 1946.
52. Peters, H. R., Guyther, J. R. and Brambel, C. E. Dicumarol in acute coronary thrombosis. *J. A. M. A.*, 398–403, 1946.
53. Wright, I. S. Experiences with dicumarol (3, 3′ methylene bis (4-hydroxycoumarin) in the treatment of coronary thrombosis with myocardial infarction. Preliminary report. *Am. Heart J.*, 32: 20–31, 1946.

Anticoagulant Therapy with Heparin*

GORDON MURRAY, M.D.
TORONTO, CANADA

WHILE the etiology of thrombosis and intravascular clotting is still obscure, the presence of this disease can make itself known in one of several mundane or melodramatic ways. The physiologic function of clotting provides for repair in the normal course of events of the vascular system and for the acute emergency of bleeding. It may be life-saving when the vessels are injured, as in external or internal hemorrhage, making this a vital function. However, if the process goes wild or under certain conditions goes into action under adverse circumstances, then instead of being a life-saving measure it may deal a death blow. The action of this function throughout the whole vascular tree, arterial, cardiac, venous and capillary, makes the possible ramifications of the manifestations of clotting a matter of very particular and significant clinical importance.

If the patient with degenerative disease of the vascular bed in the brain has the misfortune to burst a vessel, it is a matter of the greatest importance whether the clotting process can stem the hemorrhage. On the other hand, if in the coronary system a thrombosis occurs, the clot becomes a menace and the prospects for recovery depend on various circumstances which are almost beyond clinical control at the present time. If, in the vessels of the intestinal tract extensive thrombosis occurs, a mesenteric thrombosis, the patient's future is in grave doubt unless surgical interference can eradicate the disease and further thrombosis can be prevented. The benign effect of a local thrombosis in a varix of a varicose venous tree may have no more importance than the balmy breezes of early spring. However, if a similar process, either by extension or primary effect, involves the important venous trunks in the lower extremity or elsewhere, then a situation is created in which the outcome is most uncertain. Whether the lesion remains localized in this area or will shed an embolus which may be fatal, is purely a matter of accident. Again, in many surgical operations on the vascular tree, especially in the repair of arteries and in the Blalock operation, the appearance of thrombosis may be an advantage under some conditions and under others it may nullify the most careful efforts of the best surgeon and destroy the patient's hopes and prospects for benefit from surgery. The survival of the patient, the survival of the extremities and the reputation of the attending doctor may be at stake.

Because of the possible widespread manifestations of thrombosis and its complication, embolism, and because of the difficulty in defining the area involved and the level to which it has progressed, it would seem exceedingly difficult by surgical means alone to eradicate the threat of the disease. It is impossible to be sure by surgical methods alone that the condition is adequately under control. For that reason, therefore, it is suggested that an anticoagulant which reaches all remote corners of the vascular tree may have advantages under certain conditions. For example, in a patient who has a pulmonary embolism and has survived the initial shock, the prognosis may still be in doubt because of the possibility of the occur-

* From The Department of Surgery, Toronto General Hospital, Toronto, Canada.

ence of another embolism, and also because of possible extension of thrombosis in the pulmonary tree from the embolus already present. It has been well demonstrated by careful dissection of lungs in a case with one large embolus that there can be extension of this embolus to include different and more important branches of the pulmonary tree, until so much was occluded as to cause a fatal issue. This condition is completely outside the range of approach of surgery of the present day. Even though the Trendelenburg operation may remove the original embolus this must be done within a short time. If the embolus has been *in situ* for a few days and progressive thrombosis has occurred, it cannot be removed completely and the patient cannot be protected from extending thrombosis. Under these conditions we have clinical evidence that adequate anticoagulant therapy may prevent the further extension of the disease and allow the condition to heal.

While there are many anticoagulants and many different methods of application, the author's point for discussion in this paper is the administration of heparin by the intravenous drip method or intermittent injection method. While the subcutaneous method has been explored[1] and dicumarol has been administered with satisfaction, nevertheless, he will confine his remarks to the administration of heparin.

The author's experience is based on the administration of heparin experimentally in a great many animals, under various surgical procedures, and on the treatment of patients indicated as follows:

(1) Four hundred postoperative cases in which patients were treated with an anticoagulant with the object of cutting down the incidence of thrombosis and consequently of pulmonary embolism. In this group no patient developed peripheral thrombosis and there were no cases of pulmonary embolism. Our experience obviously includes too few cases to be of much significance except that the treatment was carried out in groups of patients in whom our hospital statistics showed that thrombosis and pulmonary embolism reached the highest recorded figures.

(2) Three hundred eighty-six patients with venous thrombosis in whom treatment by anticoagulants was carried out with the object of preventing pulmonary embolism and as treatment for progressive thrombosis in the venous tree with the hope of relieving symptoms and diminishing the ill effects which are so evident following venous thrombosis, such as persistent edema, varicose veins, ulceration, etc. All these patients had typical symptoms and signs of venous thrombosis before treatment was started.

The results of treatment were satisfactory in that none of the patients had pulmonary embolism; moreover, the late effects of the thrombosis were less severe than in a control group. There was less persisting edema, fewer ulcers in a nine-year period and fewer varicose veins during this time.

(3) One hundred seventy-two patients with pulmonary embolism were treated with anticoagulants. The patients were not selected and obviously were those that had survived the first embolism. In many of these the patients were in extremis at the beginning of treatment. Fifty-two presented a state which is very familiar; the patient in alarming shock, with no palpable pulse at the wrist, bordering on unconsciousness and with all the serious and dreadful effects of massive pulmonary embolism. From an analysis of histories of the hospital, together with the postmortem findings, it has been demonstrated, as shown in a previous paper,[2] that one in five of all patients surviving the first pulmonary embolism is apt to succumb to future embolisms or to the effects of propagating thrombosis.

This group of patients with pulmonary embolism which the author is reporting in-

cludes only those over whom he had control during treatment. In these he had information that the treatment was adequate and that the necessary effect on the clotting time or on the prothrombin time was obtained. He saw a fairly large number of similar cases in consultation with other doctors who undertook the treatment of the patients and for that reason these patients were not included in this report. Subsequently, the author has learned of three deaths in this group treated by other doctors. In those in whom he had control of the treatment and knew that adequate effects on the clotting and prothrombin times had been obtained, there were no deaths from embolism in 172 patients. Four of these, following the beginning of treatment, had further embolisms which were obviously of small size because they produced only slight effects upon the patient.

It is very impressive to see the effect on a patient with massive pulmonary embolism, extensive thrombophlebitis or both; the improvement that takes place in a matter of a very few hours is striking, once the effect on clotting time has been obtained. The pulmonary distress with dyspnea, pain, etc., together with the embarrassment of heart action, are diminished progressively in a relatively short time so that within a few hours there is a measurable change and within twenty-four to thirty-six hours the alarming symptoms have largely disappeared. It may take several more days before there is complete relief of all symptoms.

During the course of such treatment it has frequently been observed that there was no obvious swelling or edema of the extremities at the time of the massive embolism. However, during the course of treatment one leg would enlarge and show quite a marked edema, and on some occasions, at the same time or within a few days, the other leg would undergo similar changes. It is the author's impression from a study of the pathologic conditions that this is no indication of ineffectiveness of treatment by anticoagulants. He believes that at the time of the embolism there obviously was a massive thrombus at some site in the venous tree which was so insecurely attached that it broke off and floated off as an embolus. However, at this stage the inflammatory reaction in the wall of the vein and surrounding tissue had not reached the point where it had produced clinical symptoms. While under treatment by the anticoagulant, which can only prevent the further extension of thrombosis, the remaining thrombi have excited the inflammatory local reaction which has undergone the changes that are necessary for the healing of such a lesion.

To accomplish this effect, in the presence of thrombosis or embolism, it is absolutely essential that the original principles of application of anticoagulants be followed. First, if heparin is administered, it must be carried to the point where the clotting time of the patient is kept at or about fifteen minutes. The intravenous method of administering heparin is carried out as follows:

It may be administered as a continuous drip. The heparin may be added to saline, glucose solution or distilled water. The administration is started usually with two vials, or 20,000 units, or 200 mg. in 1,000 cc. of the solution of saline or whatever is being used. With the needle in a vein this is run in continuously at a rate of about thirty drops a minute. Before starting the intravenous infusion, the clotting time of the patient is taken. The heparin is allowed to run in until there is a measurable increase in the clotting time. The ideal situation is to have the clotting time increased to about fifteen minutes. The clotting time determinations are done every two or three hours until this rise in clotting time is detected. When the clotting time reaches fifteen minutes the rate of infusion is slowed down, probably to about twenty drops a minute, but this rate

must be adjusted according to the effect on the clotting time. When the rate of dropping is determined for the patient clotting times are done about twice a day as a check to see that things are going smoothly. Moreover, if the heparin is given following operation, the requirements as healing takes place change somewhat, so that it is necessary to perform clotting times to follow the requirement of the patient as time goes on.

The second method which we used in surgery on the blood vessels, and particularly following a Blalock or Pott's operation on the great vessels of the heart, is to have a continuous intravenous infusion of saline or other suitable solution running in; then into the rubber tube, adjacent to the needle in the vein, a quantity of heparin is injected every hour and one-half. About one hour following this injection the clotting time is taken and it should be elevated to seven or eight minutes. This, the author believes, is somewhat more safe than the continuous drip method because in the former method the rate of dropping may change and there may be alarming effects on the clotting time if this is not controlled adequately. When, however, the injection is given intermittently there is much less chance of giving an overdosage and the whole situation is under better control.

Because the effect of heparin is so evanescent it is necessary to repeat the injection at short intervals; otherwise, too large a dose must be given, raising the clotting time too high if the effect is expected to last longer than one and one-half to two hours. It is no use whatever to give heparin blindly and not know that the effect is being obtained. Since the dose is variable for the individual, the only safe way to be sure of this effect is to do clotting times at short intervals. The next principle is to give the anticoagulant until the healing process in the area of existing thrombosis has reached the stage when no further thrombosis will take place. In our experience, the average patient who is able to get out of bed should be kept at rest for three or four days under the treatment. Following this, exercise is encouraged and within six or seven days from the beginning of treatment the patient is urged to be out of bed and exercising actively. When the patient can perform this with some energy, probably on the seventh, eighth or ninth day, the heparin treatment is discontinued. If, however, the patient has some lesion or operation which necessitates staying in bed, the treatment is continued for longer periods, up to three and occasionally four weeks; for example, in such cases as spinal fusion when the patient has not been allowed out of bed. It was demonstrated experimentally that a thrombus placed in a vessel is endothelialized well within this period of time and probably that is the best protection against further extension, provided the patient has otherwise returned to normal.

CONCLUSIONS

Thrombosis and clotting may take place in any area in the vascular tree, making it difficult to be sure of effective control by surgical means alone. The universal effects of anticoagulants throughout the vascular bed suggest their value in controlling and treating this disease.

REFERENCES

1. Murray, Gordon. Heparin in thrombosis and embolism. *Brit. J. Surg.*, 27, 1940.
2. Murray, Gordon. Heparin in surgical treatment of blood vessels. *Arch. Surg.*, 40: 307–325, 1940.
3. Murray, Gordon. Heparin in thrombosis and blood vessel surgery. *Surg., Gynec. & Obst.*, 72: 340–344, 1941.
4. Jorpes, E. Der Aminozucker des Heparins. *Ztschr. f. physiol. Chem.*, 244: 253, 1936.

Conference on Therapy

The Use of Protein Hydrolysates

THESE are stenographic reports of conferences by the members of the Department of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. EPHRAIM SHORR: The protein hydrolysate is an outstanding addition to the list of therapeutic agents in recent years. It has applications in several fields of medicine and surgery, and it is for that reason that we have here today experts in these fields to discuss the various aspects of the subject. The problem of providing adequate energy for patients who are unable to take the requisite amount of foodstuffs by mouth has long been a matter of concern. For many years, parenteral alimentation was confined to the use of glucose and salts, except for the occasional and purely experimental trials of other materials, particularly fat. This was the situation until a few years ago when, as the result of the development of protein hydrolysates, it became possible to provide essential amino acids by the parenteral route. What was expected of the protein hydrolysates? Have these expectations been fulfilled? What are their uses and limitations? These are the points to be explored in the conference this afternoon. The discussion will be opened by Dr. Barr.

DR. DAVID P. BARR: As Dr. Shorr has indicated, one of the long sought goals in nutrition has been a diet which is completely adequate for maintenance and growth and which can be administered parenterally. The need is apparent in the care of all those who cannot take food by mouth or who cannot absorb ingested foodstuffs. Glucose, salts and vitamins have so long been used by injection that the technics are commonplace, but it was not until 1938 that an adequate mixture of amino acids was first successfully given by intravenous injection in humans. The story of how this came about has considerable interest. Many workers have contributed, but, I think, we owe this development chiefly to the early investigations of Robert F. Osborne and Lafayette B. Mendel at Yale and to the very long and painstaking researches of William C. Rose of the University of Illinois. The observations of Osborne and Mendel were made years ago, from about 1911 to 1914. Starting with the feeding of imperfect proteins, gliadin and zein, they discovered that two amino acids, namely, lysine and tryptophane, were essential to normal growth. Their discovery led to extensive investigations with similar methods and to the demonstration in 1928 by Rose and Cox that histidine was also essential. Shortly thereafter, Rose started research along another line, namely, that of feeding mixtures of the pure amino acids. He found that although amino acids were added to the mixtures in the proportions in which they were thought to exist in the protein, casein, they failed to support growth as well as casein itself. Rose's research led rather rapidly to a number of important discoveries: (1) In addition to the previously recognized amino acids, there was another which he called threonine and which was essential to growth; (2)

besides lysine, tryptophane and histidine, there were, including threonine, seven other amino acids apparently indispensable for growth in rats, a total of ten essential amino acids; (3) rats could grow and remain healthy without any of the other amino acids provided these ten were given; (4) while the naturally occurring amino acids were effective in nutrition, the synthetic optical isomers of some of them were ineffective.

The following ten amino acids were found to be essential in the rat: lysine, tryptophane, histidine, phenylalanine, leucine, isoleucine, threonine, methionine, valine and arginine. It was found that arginine could be formed to some extent in the body but not in sufficient amounts to support normal growth. Amino acids other than these ten can apparently be synthesized in the body or dispensed with even in the growing animal.

One of the problems which complicated Rose's investigations was the fact that many of the essential amino acids were effective in nutrition only in their naturally occurring forms. For instance, he found that dextro-histidine could be converted in the body into the naturally occurring levo-histidine. On the other hand, the levo-lysine could not be converted into the natural dextro-lysine. An immense amount of detailed investigative work was necessary to clarify the situation and to discover which amino acids had to be present in their natural form and which could be converted in the body. Rose presented an account of these researches in an important article in Physiological Reviews in 1938. He showed that in the case of the five amino acids, valine, leucine, isoleucine, lysine and threonine, only the naturally occurring forms were utilized in nutrition while their isomers were ineffective.

Still other difficulties were encountered in the use of mixtures of amino acids in nutrition. A vast amount of work was necessary to determine exactly how much of each amino acid was required to maintain growth in humans. The cost of pure amino acids was so inordinately high that few could afford the luxury of maintaining nutrition by their use. The search for substitutes, for impure mixtures, was started at once and was pursued with great energy.

As you know, three methods have been employed for obtaining impure mixtures of amino acids: (1) alkaline hydrolysis; (2) acid hydrolysis and (3) enzymatic hydrolysis. Each has presented practical difficulties. Alkaline hydrolysis is not practical because the exposure of protein to strong alkali leads to rapid racemization of the amino acids so that unnatural forms result. Acid hydrolysis leads to reactions in the mixture which destroy the essential amino acid, tryptophane. For this reason the few acid hydrolysates which are now coming on the market contain added tryptophane. The enzymatic hydrolysis is slower and less complete and produces polypeptides in addition to amino acids. There is always at least a theoretical danger of immunologically active split products of protein in an enzymatic hydrolysate.

Other practical problems arise in the preparation and administration of mixtures of amino acids. Melanin tends to form in some solutions. If the pH is not correctly adjusted, the amino acids may cause acidosis. The concentration of amino acids in solution must be so adjusted as to permit sufficient dosage without undue hydration of the body. To establish nitrogen equilibrium, dextrose must be included in appropriate amounts with the solution of amino acids.

Chief consideration should perhaps be given to the enzymatic hydrolysate which is now in most common use. Mead Johnson and Company was largely responsible for perfecting this material for parenteral ad-

ministration. As you may know, they hydrolyze the protein, casein, with pig pancreas, the enzymes of which convert both the casein and the proteins of the pancreas into amino acids and, to some extent, into the lesser peptides. The product which they call "Amigen" and which is now available in commerce, contains the essential amino acids in approximately the same percentages found in casein: lysine 5.8, tryptophane 1.0, histidine 2.0, phenylalanine 5.6, leucine 13.5, isoleucine 4.8, threonine 4.5, methionine 3.0, valine 5.0 and arginine 5.5. It is important to know that amigen contains about 12 per cent of nitrogen and that about two-thirds of it is in the form of amino acid nitrogen. In other words, 8 per cent of the amigen is amino acid nitrogen.

To Robert Elman of St. Louis, a surgeon, goes the credit for the demonstration that solutions of acid hydrolysates and of the enzymatic hydrolysate amigen can be given safely by intravenous injection in humans. The amigen is supplied in the form of a powder from which solutions may be made, but it is perhaps more satisfactory to use the solutions prepared by the manufacturer, namely, the "Amigen 5 per cent in 5 per cent dextrose solution," or the "Amigen 10 per cent solution." These are so free of pyrogens and dangerous impurities that they may be given with almost as much safety as solutions of glucose.

A liter of a 10 per cent solution of amigen, containing 100 Gm. of the hydrolysate, supplies 366 calories from amino acids and has only a little less than the caloric value of a similar weight of protein which would supply 410 calories. As in the case of protein, the hydrolysate has to be given with sufficient carbohydrate as an additional source of energy if nitrogen balance is to be attained. A solution containing equal amounts of amigen and glucose is unbalanced. Such a solution, namely, one containing 100 Gm. of amigen and 100 Gm. of glucose per liter, might be given to a patient with a very marked protein deficiency; but under such circumstances, it would probably be preferable to use plasma rather than the protein hydrolysate. For intravenous feeding over a considerable period of time, it is preferable to use each day 3,000 cc. of a solution containing 150 Gm. of amigen (544 calories) and 300 Gm. of glucose (1,230 calories), making a total of 1,774 calories per day. To this a requisite amount of salts and vitamins should be added. The following formula has been used by Albright and others: 3,000 cc. of fluid containing dextrose 300 Gm., amigen 150 Gm., sodium chloride 12.75 Gm., potassium chloride 2 Gm., vitamin C 50 mg., nicotinamide 75 mg., thiamine 5 mg., riboflavine 5 mg., pyridoxine 5 mg., vitamin K 2 mg. and calcium pantothenate 2 mg. With this as the only source of food, they were able to maintain caloric and nitrogen equilibrium over considerable periods, the quantities appearing to represent a complete feeding for a twenty-four-hour period for a person of average size. The solution is given by a continuous intravenous drip using a standard infusion apparatus. There are several difficulties which include the undesirable limitation in the activity of the patient, the need for constant attention of the doctor and the danger of venous thrombosis from prolonged injection. Intravenous alimentation of this kind must be given at a slow rate and 1,000 cc. of such a mixture should not be introduced in less than two hours. When properly administered, disagreeable reactions are surprisingly few. There may be some loss of appetite, sometimes nausea or vomiting and occasionally flushing. When oral feeding is also used, the intravenous injections should be given after meals to avoid interference with appetite. Although intravenous alimentation is always undesirable, its achieve-

ment in practical form represents a therapeutic triumph.

DR. SHORR: Dr. Glenn of the Department of Surgery will now discuss the protein hydrolysates from the standpoint of the surgical problems.

DR. FRANK GLENN: We may briefly classify surgical patients, from the standpoint of the need for proteins, into three groups, namely, those who are deficient in proteins prior to operation, those who develop the hypoproteinemia during the operation and, finally, those in whom the problem arises in the postoperative period. The first group includes patients who are unable to take food or suffer with a disturbance of the digestive apparatus giving rise to impaired absorption or losses due to other causes. In this group are to be found patients with gastrointestinal ulceration, tumors, regional ileitis and colitis. In patients with severe infection there may be reduced intake of proteins or increased destruction. Patients with hyperthyroidism may develop a protein deficiency as the result of the increased metabolism even though their protein intake be high. Patients with acute surgical conditions due to injury may develop a deficiency because of blood loss and shock. Protein loss may be very high in patients with burns. Before any surgical procedure is embarked upon in a patient with hypoproteinemia, it is of great importance to restore the protein level. The operative procedure itself may give rise to hypoproteinemia, partly as the result of hemorrhage and partly as the result of the anesthesia. The anoxia associated with anesthesia may lead to loss of plasma through increase in the permeability of the capillaries. Also, impaired metabolism of the liver cells may take place and in this way give rise to impairment in the synthesis of serum proteins. After the operation, patients lose nitrogen in excess of that of the normal individual. It is partly due to the reduced intake of food but the loss is greater than can be accounted for by this factor alone. Fever, vomiting, hemorrhage and surgical drainage all contribute to a loss of protein, but there is a decrease in nitrogen retention in patients, even without these avenues of loss. The decrease may be very considerable and may amount to from 1 to 5 pounds of body weight when they are kept in bed for a period of seven to eight days. The problem represents a wasting of muscle due to inactivity.

The loss of protein in the postoperative period is unfavorable to recovery. The hypoproteinemia affects the postoperative course in several ways: It may give rise to pulmonary edema with the increased tendency to pulmonary infection and pneumonia. It may interfere with the healing of wounds in degrees varying from slight impairment of the maturation of fibroblasts to the more extreme cases showing no tissue reaction and dehiscence of the wound. Lowered resistance to infection probably occurs indirectly through impaired detoxifying action of the liver and impaired production of the globulin fractions of proteins which are related to the immune bodies. It also promotes edema of the gastrointestinal tract following surgical procedures, and, that in turn, interferes with the functioning of stomas and restoration of the continuity in the case of gastric resections. This edema may be sufficient to prevent food from passing through stomas which are mechanically large enough. Likewise, it tends to interfere with the peristaltic action of the gastrointestinal tract.

We should pay special attention to the difficulty of determining the true content of serum proteins in the surgical patient. The protein concentration of the serum is often deceptive in the patient who has been dehydrated by vomiting or diarrhea.

A favorable nitrogen balance is of the

first importance in surgical patients. Hypoproteinemia should not be permitted to exist or develop. In the preoperative period, much may be accomplished by blood transfusions, plasma, intravenous amino acid mixtures such as amigen, and protein hydrolysates given orally. In the anemic patient, it is probably wise to discontinue the use of blood transfusions as soon as the red cell count has been restored to normal. The use of plasma for maintaining a favorable protein balance is expensive. The cost of the protein hydrolysates is more moderate. Many patients can take these by mouth if they are properly prepared. If the oral route is not feasible they may be given by intravenous injection, as described by Dr. Barr. During operation, blood transfusions and plasma are probably best for maintaining ample protein reserve. In the postoperative period, many patients require protein by intravenous injection during the first eighteen to seventy-two hours in order to maintain a nitrogen balance. This may be accomplished by the intravenous use of blood plasma or amigen. Subsequently, the protein hydrolysate may be given by mouth; and after the use of the predigested foods for a short period regular foods, which may be classified as simple from the standpoint of digestion may be resumed.

In the past, there has been a tendency to overinvalidize surgical patients, and the long period of inactivity resulted in depletion of protein stores. The pendulum is swinging in the opposite direction; and although it is wise to reduce the period of inactivity to a minimum, we should not overlook the fact that these are not normal people. The inordinate loss of proteins in the postoperative period is controlled by the present trend to mobilize patients earlier and to make use of the predigested foods shortly after operation.

DR. SHORR: Dr. Glynn, what uses do you make of protein hydrolysates in pediatric practice?

DR. MARTIN J. GLYNN, JR.: We encounter the same general indications for the use of protein hydrolysates as have been described for adult medical cases by Dr. Barr and surgical cases by Dr. Glenn. I should like to remark briefly about four conditions, perhaps more common in pediatric practice.

The youngster with severe diarrhea presents the most serious problem in which we turn to these agents. These cases are treated by prolonged starvation which in a young infant is a period of the order of two to four days. These youngsters appear to tolerate prolonged starvation quite well, but it is my impression, and that of other workers, that the use of protein hydrolysates is decidedly helpful. In the treatment of this condition, the first step is to restore the electrolyte pattern, the water balance and the plasma proteins to normal by the use of whole blood and plasma. After this is done and the circulation is in good condition, the protein hydrolysate may be given safely by hypodermoclysis. Specifically, the patient receives 40 cc. per Kg. of amigen 5 per cent in 5 per cent dextrose solution twice a day by hypodermoclysis in addition to 35 cc. per Kg. of 5 per cent dextrose solution by intravenous infusion twice a day. The treatment provides a total of 45 calories per Kg., 15 in the form of amino acid and 30 in the form of dextrose. This is by no means maintenance but it is a helpful step in that direction. I do not know of any studies on the fate of the amino acids which are provided by this regimen.

In eczema, we utilize amino acid therapy for a different purpose, namely, in an attempt to supply a source of protein with a minimum potential for allergic reactions. In severe eczemas, about 50 per cent may be expected to show considerable improvement and in some the control of the eczema

is complete. It is also worth trying in the mild eczemas of older infants. It is the impression of one observer, who tried it in mild eczemas of very young infants, that fewer of these developed severe eczema. The protein hydrolysate may be given parenterally but in eczema we are more likely to use it orally. We have used a mixture containing amino acids 20 per cent, carbohydrate up to 50 per cent, and fat 18 per cent, diluted so as to make an appropriate formula. Articles least likely to produce allergic reactions were used, in the case of the fat for example, olive oil, and in the case of the carbohydrate, arrowroot starch and dextrimaltose. Formulas based upon these materials can be made up in much the same way as the usual formula with milk so as to meet the requirements.

We occasionally use protein hydrolysates with advantage in the nephrotic syndrome. These patients often develop the so-called nephrotic crises, episodes of severe infection in the form of peritonitis, septicemia or both. We used it a great deal before the effective antibiotics were available; the intravenous amino acids seemed to influence the course favorably. A youngster who does not respond as expected to penicillin or sulfadiazine should be supported with protein hydrolysates.

There is a miscellaneous group of conditions in which amigen is often used by mouth with results that can be described as no more than encouraging. They include cases of young babies with persistent vomiting from obscure cause. A mixture containing amigen 3.5 to 5 per cent and 5 per cent carbohydrate may be given in such small amounts as are fairly well tolerated. It may be gradually replaced by the more sustaining types of nourishment. This mixture is also advocated for the first oral feedings after the therapeutic starvation in cases of diarrhea.

The other conditions, occasionally encountered in the pediatric group, are more frequently seen in adults such as postoperative troubles, trauma and burns. Their treatment is the same as in adults.

DR. BARR: It would be interesting to hear from Dr. Glenn about the use of amino acid mixtures in the treatment of burns. After a burn of moderate degree, a person may lose as much as 40 Gm. of nitrogen in twenty-four hours. The loss may continue during the ensuing days because of increased capillary permability.

DR. SHORR: The subject is now open for general discussion. I saw your hand raised, Dr. Gold.

DR. HARRY GOLD: Could we have some discussion on the matter of the utilization of amino acids? There is abundant proof that their use can establish a positive nitrogen balance, indicating that nitrogen is being retained by the body. But what is the body doing with the nitrogen? Is it converting it into the proteins which are most needed? There is an infinite number of proteins, those of the skeletal muscles, liver, blood, heart muscle and many others. The loss of proteins in disease may be due to defective supply but it may also be due to defects in the bodily mechanisms for the synthesis of specific proteins, a defect which might not be corrected by any amount of extra supply. How does the evidence stand on some of these points? Suppose we first consider the question of regeneration of blood proteins in a case of hypoproteinemia.

DR. SHORR: I have the same questions. What actually happens to hydrolysates given intravenously to a patient with severe trauma, burn, shock, operative procedures or infection? Is there any evidence that the body utilizes the nitrogen? In what condition is it not utilized? Are we justified in assuming that what goes into the vein is actually available for the nutritional requirements of the patient, particularly the very ill patient whose needs are greatest?

DR. SAMUEL Z. LEVINE: It is my understanding that Dr. Whipple has shown that the amino acids are as satisfactory as plasma in raising the plasma protein levels in dogs which have been exsanguinated by his technic. Am I correct in that, Dr. Barr?

DR. BARR: When the level of blood protein has been artificially reduced by plasmapheresis or by inadequate diet, amino acid mixtures and plasma are exceedingly effective in raising the level of serum proteins. If, on the other hand, the low level of blood proteins is due to defective formation, as in disease of the liver, the administration of plasma or of amino acid mixtures does not correct the deficiency. Neither agent is more than moderately effective in the hypoproteinemia of nephrosis.

DR. GOLD: That seems to me to be a very important point to remember. We encounter many cases of hypoproteinemia, as in advanced heart failure, cirrhosis of the liver, and other conditions, in which an intensive course of treatment with amino acids has been given. It seems to get them nowhere because the liver seems to possess no power to synthesize the protein in these conditions.

DR. GLENN: In general, we have been unable to elevate serum proteins in patients by the intravenous administration of amino acids. I have the strong belief that we can prevent patients from failing by the use of amino acids when they are unable to take food. In a patient with a lowered serum protein value, the most effective way of elevating it is by means of blood transfusions and plasma.

VISITOR: Since there are these limitations in the effectiveness of protein hydrolysates, should we rely on such methods of alimentation, or is the use of whole blood or plasma always preferable?

DR. BARR: Experience indicates that with normal animals and with normal individuals it is possible to maintain nitrogen equilibrium and normal weight solely by means of protein hydrolysates. This does not mean that the same results will be obtained in a very sick person or in a person who has been damaged by shocking experiences. Nothing that we can do by such alimentation will maintain nitrogen equilibrium in a patient with a recent colectomy or other comparably severe operation on the gastrointestinal tract. There are some observations on patients immediately after appendectomies in which fairly small infusions of hydrolysates were able to maintain nitrogen equilibrium over six-day periods. On the other hand, in the same series, patients with colectomies, gastric resections or other serious operations, similarly treated, lost nitrogen in amounts up to 140 Gm. during the same period. These observations indicate that the response which is seen in normal individuals can be duplicated in patients only if the damage or shock has not been too great.

DR. SHORR: I think you have hit the point in cases that fail to respond. The nature and the degree of stress on the organism determine the response to intravenous alimentation. Studies have been carried out in severe infection and after trauma and it has been found that all the nitrogen administered as amino acids appeared in the urine in twenty-four hours. This went on for days. One might have an illusory feeling of comfort that protein has been supplied but there is clear evidence that it is being deaminated and does not remain as protein in the organism.

DR. BARR: Are there any comparable observations on the fate of protein itself?

DR. SHORR: Yes, there are for infusions of plasma. Here the protein remains in the body longer and is degraded by a slower mechanism.

DR. BARR: Is it not excreted as urea?

DR. SHORR: It is eventually but it is released apparently so slowly as to be more

available for the maintenance of nitrogen equilibrium.

DR. WALTER MODELL: Is there any difference in the time it takes to elevate the plasma protein level by means of amino acids and of plasma infusions, assuming, of course, a case in which either one or the other may do it?

DR. BARR: I do not think there is very much difference.

DR. SHORR: Might it not depend, Dr. Barr, on the state of the subject? In the normal animal in which the plasmapheresis experiments were conducted, all the normal capacities to synthesize proteins from amino acids were retained whereas in patients, suffering with a variety of infections or wounds, varying degrees of defects in the capacity for protein synthesis might obtain. Under such conditions the organism may hold on to injected plasma proteins so that the blood level can be satisfactorily raised, whereas injected amino acids may be much less efficiently utilized.

In relation to your point, Dr. Gold, that the retention of nitrogen after the administration of amino acids is an established fact, it is well to remember that in many cases neither oral nor parenteral administration of the usual amounts of protein in the diet gives rise to a positive balance. It is only after extraordinary amounts such as Co Tui, for example, used in his patients after gastrectomy, 350 to 450 Gm. of protein per day, that a positive balance appeared. As I have already indicated, in the patient with disease, receiving a parenteral infusion of amigen calculated to maintain a protein balance, every bit of the nitrogen often comes out in the urine within the same day in the form of ammonia or urea. There is a problem here which remains unsettled. Of course, it has nothing to do with the usefulness of this procedure as supplementary to oral feeding. But it does bring up the question of what is the nature of the disturbance in disease which is responsible for such rapid breakdown and wastage of nitrogenous materials.

DR. BARR: I should like to hear from Dr. Shorr some comment as to the reason for the tremendous loss of protein which occurs following injury such as fractures, burns, acute infectious diseases or almost any other insult to the body. There are records of patients who during a ten-day period after operation have lost as much as 100 to 180 Gm. of nitrogen corresponding to 2.5 to 4.5 Kg. of muscle. A surprisingly great loss occurs often in uncomplicated anesthesia. Why should the body lose nitrogen under such circumstances?

DR. SHORR: It would be very nice if there were an answer. There are a number of possible explanations. One clinical observation may be cited, namely, that patients may or may not lose protein excessively under these circumstances and that, whether they do so or not, depends on their nutritional state; a highly undernourished individual may undergo an experience of this sort without loss of protein. Cuthbertson showed this very clearly in his experimental animals. Why does the debilitated individual not lose protein when the well nourished person may have a negative nitrogen balance of 30 Gm. on a daily ration of 150 Gm.? This possibly requires invoking the concept that there is one type of protein which is a little more specifically a part of the chemical structure of the cell, and another type which is, shall we say, in the nature of a reserve or depot protein in the old-fashioned sense. It would look as if the debilitated individual were down to his basic protein stores and for that reason does not readily lose more protein while the well nourished individual readily loses protein to the extent of his extra protein reserves. In addition, hormonal factors may play a rôle. This process which takes place in the course of the first three weeks after an

insult, such as infection or a fracture with recovery, may involve the action of hormones which have to do with protein metabolism and the reparative process, namely, the glycotropic and androgenic adrenal cortical hormones. It has been shown by Selye that, after any kind of stress or damage, an extraordinary change in the adrenal cortex takes place; it looks as if one had completely released its lipoids and with them its cortical hormonal content. Under the influence of stress, it is known that certain of these hormones are capable of breaking down protein excessively and forming carbohydrate from the non-nitrogenous residues. Support for this concept has been supplied for the human by Browne and his associates. These cortical hormones have been found by Venning and Browne in the urine in great excess after infections such as pneumonia, after operations, after fractures and, in fact, after all manner of stress and exposure.

Testosterone and its end products, the 17-ketosteroids, which we also measure in urine, have been demonstrated by Kenyon and others to promote the storage of proteins. Individuals who receive these androgens store protein unusually well, both normal individuals and those who have a lack of androgenic hormones such as hypogonadal males. It has been found that the level of 17-ketosteroids is characteristically low during the phases of an illness or damage when the level of adrenal cortical hormones is high. It looks as if these two factors, a depression in the elaboration of protein-storing hormones and an increase in the elaboration of protein-degrading hormones, may play a part in the unusual loss of protein during recovery.

DR. BARR: Much emphasis is now given to the loss of serum proteins which takes place during short periods. Surgeons, particularly, have regarded such loss as justification for protein administration and for reasons which Dr. Glenn has brought out very clearly. One wonders, however, whether the consequences which are feared actually occur and whether it is so dreadful for the protein of the circulating blood to fall by 10 per cent, which will happen after forty-eight hours of starvation, and whether such a mishap must be corrected at once by the administration of plasma, albumin or amino acids. I doubt whether the actual necessity has been demonstrated but I should like to hear Dr. Glenn's opinion.

DR. GLENN: I think that the loss of a certain amount of protein in the normal individual, as Dr. Barr says, is probably not of great importance, but in an individual who is already depleted the further lowering may cause trouble and may account for the difference between a wound that will heal and one that will not. I believe that the intravenous administration of proteins exercises a type of sparing action.

DR. SHORR: I am inclined to agree that there is very little proof that a small reduction in blood proteins seen in surgical cases is of importance and that we may be going too far in our measures to correct them. It would seem reasonable, however, to attempt to restore blood proteins in cases in which they have fallen considerably. There is another question, however, which needs consideration, namely, how far we should go in attempting to establish a positive nitrogen balance in patients whose plasma protein levels are normal. Consider, for example, the patients with peptic ulcer who are now treated with amino acids. Vast quantities are necessary to establish a positive nitrogen balance in some of these. Is the positive nitrogen balance established in such cases beneficial to the course of the disease? I do not believe that we have the answer to this question. It certainly can be said that patients with fracture recover and

do extremely well at a time when they have regained only a small fraction of the protein lost during the illness.

DR. MCKEEN CATTELL: The use of amigen has been extensively discussed. I want to ask whether other protein hydrolysates which are available are not equally satisfactory, or is there some preference for this particular brand.

DR. BARR: It is quite probable that the mixture which is called "Amigen" may be duplicated or improved. Many similar preparations have been offered and are now undergoing clinical trial. Since there are many pitfalls in the preparation of amino acid mixtures, actual clinical experience is needed with each new product and it is becoming increasingly difficult to find investigators who are interested in testing a new mixture to determine whether it is as good as one which is known to be satisfactory. Many tests are necessary. Ability to support normal growth must be demonstrated. Absence of immunologically active fractions must be established. Since mixtures of amino acids furnish an excellent culture medium, bacterial contamination must be excluded. Finally, the solutions must be free of pyrogens and other impurities. I mention these requirements to indicate how difficult it is to be sure that a new preparation of a protein hydrolysate is as satisfactory as one which has already been tested.

I think that Dr. Almy has had some experience with an acid hydrolysate.

DR. THOMAS P. ALMY: We used the preparation of Stearns and Company, parenamine 6 per cent, in two patients. It was well tolerated when injected at a rate similar to the rate at which we administer amigen. It is more acid than the parenteral amigen preparation; the pH is 5.5.

DR. SHORR: Perhaps Mr. Clarke, our pharmacist, would say something about the various preparations now available.

MR. DONALD A. CLARKE: The following list of preparations is presented with the stipulation that it will probably be out-of-date in the near future, for not only are new preparations being added but the old ones are being altered.

I know of only two acid hydrolysates, parenamine (Stearns), made from casein, and aminosal (Abbott) made from beef-blood fibrin, both intended for parenteral use. No alkaline hydrolysate is available. All the others are enzymatic hydrolysates. Amigen (Mead Johnson) which is made from casein has already been mentioned. It is presently available only for parenteral use although the original preparation was also used orally. Their oral preparation is called protolysate, made from casein. Here is a partial list of other oral preparations: aminoids (Arlington) from milk, beef, wheat and yeast; aminoprote (U. S. Vitamin) from beef, casein, lactalbumin and yeast; lactamin (Wyeth) from lactalbumin; ledinac (Lederle) from liver; protein hydrolysate-MRT (Thompson) from yeast; protein hydrolysate (Squibb) from casein. Some of these preparations are already mixed with some form of carbohydrate. There are many other preparations not listed, which contain, in addition to hydrolyzed protein of some kind and carbohydrate, some other substances such as minerals, vitamins, flavoring materials and in one case, olive oil.

The parenteral preparations are usually provided as sterile solutions with added dextrose. Several concentrations of each are generally available, usually in the range from 5 to 10 per cent. The oral preparations are most commonly available in the form of a powder, some in the form of granules. Flavored solutions are obtainable and one manufacturer supplies an enteric-coated tablet.

DR. GOLD: It might be worth while calling attention to the fact that there are protein hydrolysates on the market sub-

stantially free of sodium chloride. This is of some importance in the problem of feeding a patient with congestive failure. I know of one such preparation, protein hydrolysate-MRT. It is not to be confused with the other preparation by the same manufacturer which contains 6 per cent sodium chloride. There is another preparation called protinal (National Drug) which is said to be very low in sodium chloride. There are other similar preparations.

In connection with the choice of preparations, it might be worth mentioning the experimental observation that the composition of a mixture of amino acids has a bearing on the extent to which it is utilized in the body to form proteins. It has been shown that if one omits an essential amino acid, an otherwise adequate mixture will fail to be utilized, and that the defect in utilization cannot be corrected if several hours elapse before the missing amino acid is supplied. This is a challenge to the preparations of protein hydrolysates; a proper mixture must be made available to the tissues at the same time if the mixture is to prove effective. This is perhaps one of the reasons why, as Dr. Barr has pointed out, it is necessary to test a new hydrolysate for its capacity to support growth. This may also have bearing on the question of the utility of protein hydrolysates in patients with evidence of protein deficiency who may be able to consume large quantities of proteins in the form of ordinary foods. We do not have satisfactory clinical evidence concerning this point; but it must be considered as a possibility that such patients may suffer with difficulty in protein digestion, so that an adequate mixture of amino acids does not become available in the blood stream, adequate in the sense of relative proportions of different amino acids being present at the proper time to enable the tissues to utilize them for the synthesis of tissue proteins.

Dr. Charles H. Wheeler: From talking with the house officers sometime ago, Dr. Barr, I gained the impression that they were still dissatisfied with the solutions of amigen. There were frequent pyrogenic reactions. Am I misinformed about that?

Dr. Barr: When Elman started to use amigen, he encountered some quite alarming reactions consisting of fever, nausea and vomiting. As preparations improved and the rate of injection was slowed, he finally attained a record of the injection of many liters without any reactions. The absence of pyrogens in the solution and slow injection are factors of the greatest importance in the avoidance of reactions.

Dr. Levine: The experience at Washington University has been very satisfactory. Intravenous and subcutaneous injections have been given to a large number of infants and young children without significant reactions. Our early experiences in smaller numbers were not so favorable. The children developed fever and some went into collapse. The house staff had become reluctant to use it. Matters have improved, however, with the more recent preparations and slower injections.

Dr. Gold: It seems from the literature that the number of serious accidents following parenteral amino acid injections is not very large. There was a report by Curreri and associates in the Journal of the A.M.A., July 7, 1945, in which they encountered one fatality after about 2,000 administrations. The patient received the intravenous infusion of the usual preparation for two days without trouble but on the third day developed a shock-like reaction with hyperthermia and died forty hours later. They stressed the desirability of making someone in the hospital responsible for supervision of these infusions in order to insure that the solution is clear, that the rate of injection is slow, that the amino acid solutions are not mixed with materials of high pH, such as sodium salts of the sulfa drugs which give

rise to precipitation, and that the unused contents of the bottle which has been opened should be discarded. There seems to be the possibility that bacterial contamination in open bottles may give rise to toxic amines. Bacterial contamination is one of the points which Dr. Barr has stressed.

VISITOR: Has there been any sloughing in the case of the hypodermoclysis?

DR. GLYNN: We encountered one case of extensive sloughing in approximately 1,000 such treatments.

DR. GOLD: In regard to the toxicity of amino acids, you may be interested in some observations which were made by Riker and myself a few years ago in a study of sodium hydroxyacetate in which we also tested the amino acid, glycine. One is inclined to regard the amino acids as harmless since they are essential products of normal metabolism, however, we discovered that glycine may act as a poison in cats and dogs; as little as 1 Gm. per Kg. intravenously in cats gave rise to drooling, muscular weakness, hyperexcitability and dilatation of the pupils with failure to respond to light; and an oral dose of 6 Gm. per Kg. in a dog caused similar symptoms with convulsions and death in four hours. Clearly, the amino acids are not harmless substances.

DR. SHORR: What has been your experience with reactions, Dr. Almy, in the management of ulcerative colitis in which the intravenous route was used?

DR. ALMY: Our experience in one patient has been grim. Alimentation exclusively by intravenous route for a week resulted in thrombosis of all accessible veins. I was told by Dr. Albright that if one escapes this difficulty, one may begin to see remission of the acute symptoms with this treatment after one week.

DR. BARR: It might be interesting to hear of Dr. Almy's experience with the oral use of the amino acids in ulcerative colitis. The discussion thus far has dealt chiefly with intravenous alimentation which, perhaps, has less application than the oral route.

DR. ALMY: In ulcerative colitis, the intravenous administration of hydrolysates has always appeared more attractive because of the fact that it avoids the use of the colon as a conduit of food residue, however, we have tried large amounts of the hydrolysate orally in these protein-starved patients. We gave them 5 to 6 Gm. of amigen per Kg. per day by mouth, together with dextrimaltose in a manner comparable to that used by Co Tui in the treatment of peptic ulcer. The results were not as striking as I had hoped they would be. In a small group of a dozen patients, 30 per cent showed a rapid gain in weight to the extent of about 3 to 5 Kg. and progressive improvement resulted. The other cases remained uninfluenced. This form of alimentation caused severe diarrhea in these patients and it is noteworthy that in spite of it the gain in weight took place.

VISITOR: How successful is the retention enema of amigen?

DR. FREDDY HOMBURGER: We have been using retention enemas of a Squibb casein hydrolysate which is roughly comparable to amigen and, when given with proper technic and care, have achieved positive nitrogen balance over a fairly long period of time. It was not found possible to achieve this in all patients but in about one-third of the patients it was successful.

DR. SHORR: And what is the proper technic?

DR. HOMBURGER: The rectum should first be cleansed very carefully with a small water enema. Only small quantities at a time should be used. Instead of the ordinary rectal tube a urethral catheter should be inserted to about 10 or 12 inches. We use a Murphy drip for about one to two hours to give 400 cc. of the solution which contains about 100 to 150 Gm. of hydrolysate in 5 per cent dextrose. Usually the first day there

is some irritation; but when the patient is accustomed to the procedure, the enema may be retained and nitrogen balance may be maintained.

DR. SHORR: Where do you think the resorption takes place? In what part of the large gut?

DR. HOMBURGER: I think that the resorption takes place in the lower portion of the large intestine where water is known to be resorbed.

DR. SHORR: Not in the rectum?

DR. HOMBURGER: In the sigmoid, I think. We have evidence only for the fact that the nitrogen contained in the administered material is retained.

DR. GOLD: The protein hydrolysates may therefore be given by various routes, oral, subcutaneous, rectal and intravenous. There are reports of its satisfactory use by the intrasternal route directly into the bone marrow by means of the Turkel needle. The needle may apparently be left in place for twenty-four hours or longer and the material may be administered as rapidly by this route as by the intravenous route, about 1 to 2 Gm. of amino acid nitrogen per hour.

DR. SHORR: This is an extensive subject and there are many more points which need to be considered but our time is up. Perhaps the interesting topic of protein hydrolysates in peptic ulcer may be taken up at another conference.

SUMMARY

DR. GOLD: We may now bring together a few of the salient points which were elaborated in the conference this afternoon. A disorder of protein metabolism seems to be extremely common in diseases, injuries and other states of bodily stress, such as infections, operations, anesthesias, malignancy, burns, hyperthyroid states, diarrheas and prolonged inactivity. It is clearly manifest when there is extensive body wasting, but it is earlier detected by an increased loss of nitrogen of varying degrees often reaching alarming proportions. The circumstances are frequently such that an adequate supply of proteins in the form of the usual foods and the use of the regular channels for their consumption are not feasible. Great interest has, therefore, been aroused in the discovery about ten years ago that it is possible to prepare appropriate mixtures of amino acids in the form of protein hydrolysates, suitable for all the common routes of administration, and to use them as a source of bodily proteins. It appears to be a development of major importance, the culmination of experiments covering a period of nearly forty years. It supplies the missing link, the protein, the others being carbohydrates, fats and vitamins, in the long quest for complete intravenous alimentation.

There was not sufficient time to consider all the conditions in which the protein hydrolysates may be applied, but the discussion indicates that they have already been put to use extensively in a wide variety of conditions associated with an unfavorable protein balance. In the conference, the surgeon discussed their uses preoperatively and postoperatively in relation to extensive surgical procedures, traumas, hemorrhage and anesthesia. The pediatricians discussed their value in the treatment of diarrheas of infants, in the nephrotic syndrome and in eczema as a source of protein with minimum potential for allergic reactions. They seem to be of great value in patients with burns who lose alarming quantities of protein, of some value in edema associated with hypoproteinemia, in ulcerative colitis, peptic ulcer and in nutritional problems in which only parenteral alimentation is feasible. This is but a small part of the list of conditions in which the protein hydrolysates have been recommended and used as a means of promoting recovery from states of ill health.

Enthusiasm for the use of protein hydroly-

sates has naturally run very high; and as experience has increased and the problem has received more intensive consideration, numerous questions have arisen. How strong is the evidence for the utility of the protein hydrolysates in a large proportion of the conditions in which they are now used? Are we assigning too many troubles to the moderate reductions in blood protein levels and negative nitrogen balance which occur so commonly? Is the zeal for establishing nitrogen equilibrium or positive nitrogen balance in many of the conditions in which they are now used justified by the results? Since such restorations seem theoretically correct, there is the danger of carrying the application of protein hydrolysates far beyond the point of satisfactory evidence that they are actually useful.

On the theoretical side such questions have been raised as to what the body does with the amino acids administered in the form of protein hydrolysates. In normal individuals, the evidence is strong that, when they are administered sufficiently slowly and in proper composition, they are stored and converted into proteins; but much remains to be learned about abnormal states in which the basic difficulties may lie in defective mechanisms for converting amino acids into the infinite number of proteins. Then there is the question whether the administration of hydrolysates serves merely to spare body proteins or whether they exert some other type of beneficial actions. Why does the body lose protein so rapidly in such conditions as protracted bed rest, anesthesia and operative procedures in which there may be apparently little blood loss or tissue destruction? An interesting viewpoint was presented to the effect that an endocrine imbalance involving the cortical hormones of the adrenal and the androgens may be responsible for the marked loss of proteins in certain states of bodily stress.

The answers to some of these questions have not been entirely satisfactory, but the exploration of these and others in the discussion this afternoon has helped to reveal the complexity of the problem and to provide some insight into the reasons for the numerous failures to accomplish expected results. In disease states, the simple loading of the system with amino acids falls far short of correcting many of the conditions. It was pointed out, for example, that hypoproteinemia in surgical problems is much more often corrected by plasma or blood infusions than by intravenous hydrolysates; and that in the prolonged starvation in infant diarrhea, it is imperative first to restore the blood protein level by plasma infusions before attempting to maintain the gains by parenteral protein hydrolysates. Much careful observation will be necessary properly to sift out the practical from the large volume of theoretical indications.

The parenteral administration of protein hydrolysates is not without risks. The improvement in the preparations of commerce and the slowing of the rate of administration have greatly reduced serious accidents although minor unpleasant reactions are fairly common. Suggestions have been made for avoiding disasters in the routine use of intravenous protein hydrolysates in hospital practice.

The choice of preparations is of considerable importance, especially in relation to those for intravenous injection. Many of the preparations now on the market show great improvement in composition, freedom from pyrogens and allergenic peptides, but the matter of preparations is in a state of constant flux; the ideal preparation is not yet available.

The discussion also includes such topics as a formula for complete intravenous alimentation, dosage for oral use and the various routes of administration.

Clinico-pathologic Conference

Hydrohemothorax and Peripheral Vascular Collapse*

STENOGRAPHIC reports, edited by Robert J. Glaser, M. D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, W. K. (B. H. No. 137472), a seventy-two year old white, unemployed male, entered the Washington University Clinics on July 3, 1946, complaining of cough. The family history was entirely normal. The past history revealed that in his youth, the patient had had measles and, for a month thereafter, a severe cough. Since that time he had been subject to upper respiratory infections which were usually associated with cough. The patient first had malaria when thirty-six years of age and then had had several subsequent attacks. At the age of forty-seven, he contracted typhoid fever but made an uneventful recovery. He always had been obese and at one time weighed 274 pounds. He had worked in a machine shop until forced to retire one year before admission because of his age. His habits were good.

Two months prior to entry, the patient was out in the rain for several hours; that night his chest felt somewhat "tight" and he wheezed slightly. He then developed a persistent cough, productive of small amounts of frothy sputum which was sometimes "tinged with pink" and occasionally contained a little gross blood. The sensation of tightness in the chest increased and wheezing became audible; the patient was of the opinion that the wheezing originated in the right side more than in the left side of his chest. He had no pain but noted increasing shortness of breath on exertion and after coughing. His appetite steadily failed and he began to have night sweats. Since the onset of his illness, he had lost 14 pounds.

Physical examination on entry revealed the temperature to be 36.8°C., the pulse 88, respirations 22, and blood pressure 140/100. The patient was markedly obese; he wheezed audibly on expiration but was not orthopneic. The pupils reacted normally; the fundi showed some arteriolar narrowing. The ear drums were retracted and hearing was slightly impaired. There was a large perforation of the anterior nasal septum and the nasal mucosa was red and edematous. The tonsils were atrophic. The trachea was in the midline. The right side of the chest appeared to be flatter than the left and moved less well. There was flatness to percussion over the lower half of the right chest anteriorly and posteriorly; over this area tactile fremitus was lost and breath sounds were absent. Breath sounds were bronchial in quality over the right upper lobe anteriorly. The spoken voice was diminished over the right lower lobe and had a nasal quality; the whispered voice was

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

absent. The cardiac apical impulse was not felt and the left border, which was percussed with difficulty because of the patient's obesity, extended approximately 13.5 cm. to the left of the mid-sternal line in the fifth interspace. The rhythm was regular; the sounds were very distant but P_2 was greater than A_2. The abdomen was pendulous but no organs or masses were detected. In the left upper portion of the prostate a small, very firm, non-tender nodule was palpable. The deep tendon reflexes were hypoactive.

A roentgenogram of the chest was reported as follows: "There is fluid in the right pleural cavity up to the third interspace; the heart is shifted to the left. The left chest is clear."

The patient returned to the Clinic three days after his first visit; a thoracentesis was performed and 1,300 cc. of serosanguineous fluid were removed from the right chest. The fluid did not clot; it contained 35,000 cells without acid and 1,300 cells with acid; the differential count showed 52 per cent lymphocytes, 16 per cent segmented forms and 32 per cent large mononuclear cells.

The patient again returned to the Clinic three days later in apparent shock. He was immediately admitted to the Barnes Hospital. No further history was available.

At the time of entry, physical examination revealed the temperature to be 36.5°c., the pulse 110, respirations 40 and the blood pressure 80/0. The patient was pale, perspiring and markedly dyspneic and orthopneic. He talked in gasps but the effort seemed to exhaust him. The trachea was displaced to the left. An inspiratory wheeze was audible and expiration was forced. A paradoxical pulse was present. The liver edge was felt 2 cm. below the costal margin and was slightly tender. There was pretibial edema. The remainder of the physical examination was unchanged from that recorded previously.

The laboratory findings were as follows: Blood count: red cells, 5,240,000; hemoglobin, 15 Gm.; white cells, 19,650; differential count: segmented forms, 77 per cent; lymphocytes, 12 per cent; monocytes, 11 per cent. Urinalysis: albumin, normal; sediment: many hyaline, finely granular and waxy casts; 20 to 30 red blood cells per high power field. Blood Kahn reaction: negative. Roentgenogram of the chest: "There is some increase in fluid in the right pleural cavity since the previous film. A fluid level is seen within the circle of the first rib. There is little displacement of the mediastinum; the cardiac shadow is enlarged." Electrocardiogram: Low voltage in all complexes; T waves iso-electric in leads I, II, and III; Q wave in leads III and CF IV.

Immediately after entry, a thoracentesis was performed; after 1,250 cc. of serosanguineous fluid were removed from the right chest, the patient became more dyspneic and anxious and the procedure was discontinued. The fluid had a specific gravity of 1.014; it contained 70,000 red cells and 2,050 white cells. The differential count showed 3 per cent segmented forms, 95 per cent lymphocytes and 2 per cent large mononuclear cells. The protein content was 2.4 Gm. per cent. Microscopic sections of the cell block sediment (reported after death) revealed epithelial cells which formed acini. Roentgenogram of the chest, obtained following the thoracentesis, was reported as follows: "There is a large amount of fluid in the right chest; the trachea is deviated to the left in its upper portion and to the right in its lower portion. The heart is unchanged in appearance from the previous film. The left chest is clear."

Following the thoracentesis the patient continued to be markedly dyspneic and orthopneic; he was given 30 mg. of morphine sulfate in divided doses and was placed in an oxygen tent. The heart sounds became inaudible; the pulse was thready but definitely paradoxical. The respirations

became progressively more difficult and rapid. Twelve hours after admission another thoracentesis was done on the right, and 600 cc. of serosanguineous fluid were removed without obvious benefit to the patient. A pericardial paracentesis was attempted and 50 cc. of bloody fluid were withdrawn; the fluid did not clot. The patient continued to fail and died twenty-four hours after admission.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case presents two major problems: The first concerns the nature of the primary disease and the second the explanation of the terminal events. When the patient first came to the Clinic, he was not desperately ill; he became so, however, several days later and died within a week. Dr. Flance, what primary diagnosis would you attach to this man's illness?

DR. I. JEROME FLANCE: Considering the patient's age, his history and the fact that he had a bloody pleural effusion, it seems likely that he had a malignancy and one would certainly consider the possibility of primary carcinoma of the lung.

DR. ALEXANDER: Dr. Dammin, would you describe the microscopic section made from the cell sediment of the pleural fluid?

DR. GUSTAVE J. DAMMIN: One sees two types of cells in the section. (Fig. 1.) The darker staining cells appear to form acini and thus strongly suggest a malignancy. The lighter cells with large pale nuclei constitute the normal lining of the pleural surface. In our opinion, the most likely diagnosis is that of a malignant tumor involving the pleural cavity.

DR. ALEXANDER: Dr. Flance, would you comment on the type of tumor which this man may have had?

DR. FLANCE: Primary adenocarcinoma of the lung usually does not occlude a major bronchus whereas squamous cell carcinoma may well cause bronchial obstruction. The signs described in the physical examination would have been compatible with bronchial obstruction in addition to pleural effusion.

DR. ALEXANDER: Is adenocarcinoma the most common type of primary lung tumor?

DR. FLANCE: No, epidermoid carcinoma is most frequent. The fact that such tumors often arise around a major bronchus explains why they may ultimately lead to obstruction and atelectasis.

DR. ALEXANDER: I understand that you assume that the pleura was invaded by a tumor which was primary in the lung. Have you considered a primary endothelioma of the pleura?

DR. FLANCE: It is an extremely rare tumor.

DR. ALEXANDER: I agree that it is most likely that this man had a bronchogenic carcinoma which invaded his pleura and gave rise to the effusion. A thoracentesis was performed and 1,300 cc. of fluid were removed. Three days later, when the patient was admitted to the hospital, another thoracentesis was begun and 1,200 cc. of fluid were removed before the procedure had to be interrupted because of increasing dyspnea and apprehensiveness. Is rapid reaccumulation of fluid common in a situation such as was presented here?

DR. FLANCE: Patients with metastases to the pleura may reaccumulate fluid with striking rapidity.

DR. ALEXANDER: Is not the fact that the effusion was bloody of great significance in regard to prognosis?

DR. KEITH S. WILSON: A number of studies have shown that most bloody pleural effusions are due to malignancy involving the pleura. A certain number arise as a result of direct trauma or rupture of a vessel and rarer causes include tuberculosis and acute infections of the lung.

DR. ALEXANDER: Turning to the events which led to the patient's admission to the

hospital, it will be remembered that when he returned to the Clinic for the third time, his condition had become grave; indeed, he was described as being in shock. Dr. Wilson, I believe you saw him at that time. Would you comment?

DR. WILSON: He certainly appeared to be in a state of peripheral vascular collapse. We felt that in all probability he had a pericardial effusion, probably with tamponade.

DR. ALEXANDER: Dr. Bottom, do the x-ray findings contribute to the solution of the problem here?

DR. DONALD S. BOTTOM: The second film was obtained with portable equipment and was not very clear but the heart did not seem to be larger than it was on the previous films and the mediastinum did not appear to be shifted.

DR. ALEXANDER: Dr. Schroeder, do you believe that a massive pleural effusion may give rise to signs simulating cardiac tamponade?

DR. HENRY A. SCHROEDER: No, I do not think so, especially if the mediastinum is not shifted.

DR. ALEXANDER: Dr. Wilson, what signs pointed to cardiac tamponade?

DR. WILSON: The inaudible heart sounds, paradoxical pulse and shock-like state all suggested that diagnosis.

DR. ALEXANDER: Dr. Erlanger, would you discuss the electrocardiogram? Does it give any indication of cardiac tamponade?

DR. HERMAN ERLANGER: The most striking thing about the electrocardiogram was the extremely low voltage; the T waves throughout were flat. The extremely low voltage and the flattening of the T waves are both consistent with a diagnosis of pericardial effusion and taken together with the physical signs and the patient's clinical condition are certainly significant. If the patient had had pericarditis, elevation of the S-T segments with inversion of the T waves might have been present.

VISITING PHYSICIAN: Were the patient's veins distended?

DR. WILSON: The patient was quite obese and neck vein distention could not be demonstrated.

DR. ALEXANDER: Is venous distention prominent in acute tamponade?

DR. WILSON: Frequently it is not; the venous pressure should be measured in order to determine increased venous pressure; often, as was true here, patients are so dyspneic and apprehensive that accurate determinations cannot be made.

DR. ALEXANDER: In chronic constrictive pericarditis there are adhesions about the vena cavae causing the venous pressure to be elevated, but in acute tamponade I am not quite certain as to the mechanism. The pericardium does not extend far over the veins entering the right auricle and one must consider pressure on the auricle itself.

DR. WILSON: In chronic constrictive pericarditis, I would expect the venous pressure to be considerably higher than in acute cardiac tamponade.

DR. SCHROEDER: One must take into account the amount of fluid remaining in the peripheral vascular system at the time of the cardiac accident. For example, in cardiac failure associated with coronary artery occlusion, the venous pressure may not be elevated at the onset, but as time goes on, especially in the presence of severe occlusion, and the patient retains salt and fluid, the amount of fluid in the periphery increases and the signs of congestive failure appear.

DR. DAMMIN: Do you interpret the palpable liver and the pretibial edema as evidence of impaired return of blood to the right heart?

DR. SCHROEDER: Yes.

DR. HENRY H. GRAHAM: Three days before entry, when the patient was examined in the Clinic, his liver was not palpable and he apparently had no edema; he did, however, have edema when admitted to the hospital.

VISITING PHYSICIAN: If this patient had not been in shock when he came in, his venous pressure might well have been elevated.

DR. SCHROEDER: That is a very well taken point. The extra fluid may have been in his capillaries.

DR. SAMUEL C. BUKANTZ: I think we should consider the large amount of fluid in his right chest as possibly accounting for the low circulating volume, especially if the effusion represented a recent and fairly rapid accumulation.

DR. ALEXANDER: The patient had a total of about 2,500 cc. of fluid removed from his chest. I do not know whether this amount could have been a factor in his low circulating blood volume. What is your opinion, Dr. Schroeder?

DR. SCHROEDER: It is difficult to say. I think that this loss of fluid from his vascular system would have been replaced by congestive fluid. However, if the patient had received no fluid by mouth or vein, he may well have been dehydrated.

DR. ALEXANDER: Are there any other suggestions to explain the acute episode which lasted only twenty-four hours and terminated in the patient's death?

DR. PALMER H. FUTCHER: I think of one alternate possibility—coronary occlusion. This man was seventy-two years old and was certainly a candidate for coronary artery disease; I do not believe that the electrocardiogram rules out the possibility of an acute myocardial infarction.

DR. ALEXANDER: How would you explain the pericardial fluid which apparently was not present one week prior to death?

DR. FUTCHER: If the patient had had a coronary occlusion, he might well have had a small amount of pericardial fluid in association with the acute episode. Only 50 cc. of fluid were withdrawn from the pericardium; such an amount, if indeed that is all there was, would have been insufficient to cause tamponade.

DR. ALEXANDER: Dr. Graham, are you satisfied that there were only 50 cc. of fluid in the pericardium?

DR. GRAHAM: No, I am sure there was much more.

DR. ALEXANDER: What alternate explanation do you offer for the pericardial fluid?

DR. FUTCHER: The patient may have had local involvement of the pericardium by tumor; it is also conceivable that the needle was not in the pericardial sac when the 50 cc. of fluid were withdrawn.

DR. ALEXANDER: Certainly, a tumor of the lung may have metastasized to the pericardium and given rise to an effusion.

DR. FUTCHER: In considering the origin of metastatic carcinoma, two sites come to mind, neither of which seems as likely as the lung. First, the presence of red cells in the urine suggests a renal call carcinoma. Secondly, a small nodule was described in the prostate and conceivably the patient may have had carcinoma of the prostate with metastases.

DR. ALEXANDER: I think both of your suggestions merit consideration. Hypernephroma, which so frequently metastasizes to the lungs, is particularly worthy of consideration.

DR. SCHROEDER: Could we have additional information regarding the nature of the fluid taken from the pericardium?

DR. GRAHAM: The fluid looked like pure blood but did not clot.

DR. ALEXANDER: Are there further suggestions?

DR. ERLANGER: There is one further comment which I would like to make. The electrocardiogram does not rule out the possibility of myocardial infarction. In the early stages of an infarct, the electrocardiogram may show very little change other than low voltage.

DR. ALEXANDER: In summary, it seems most likely that this patient had a bronchogenic carcinoma which metastasized to the right pleural cavity and probably to the pericardium; the pericardial metastases produced an effusion and subsequently cardiac tamponade of rather sudden onset. Acute myocardial infarction has been mentioned as a possible explanation of the terminal episode and the kidney and prostate were listed as possible primary tumor sites.

Clinical Diagnoses: Bronchogenic carcinoma with metastases to the right pleural cavity and the pericardium; pericardial effusion and acute cardiac tamponade; ? myocardial infarction; ? hypernephroma; ? carcinoma of the prostate.

PATHOLOGIC DISCUSSION

DR. RICHARD E. JOHNSON: The right pleural cavity contained 300 cc. of blood-stained, cloudy fluid. In the right upper lobe there was a marked retraction of the pleura over an area approximately 1 cm. in diameter. The cut surface through this area revealed a grayish, granular tumor mass lying immediately beneath the retracted pleura, and a white zone of induration extended toward the hilus also involving the mediastinum. The main stem bronchus was narrowed by a thickened, indurated wall but the mucosa, as far as it could be traced, was intact. A small bronchus, approximately 1 mm. in diameter, entered the tumor mass and ended in an area of necrosis. A lingular process of the right lobe was cut off by fibrous scarring and the area was reddened and firm. A small artery leading to this region was found to contain a grayish-red thrombus. The left lung showed many areas of atelectasis.

The pericardial sac contained 1,500 cc. of grossly bloody fluid which did not clot. The parietal layer was continuous with the tumor mass in the mediastinum and its surface was covered with a shaggy fibrinous exudate. When the exudate was removed, the surface was finely granular with many grayish white nodules and extensive areas of ecchymosis. There were two nodules noted in the liver and a single small nodule in the cortex of the right kidney. They were interpreted as representing metastatic tumor.

In the posterior lobe of the prostate, there was a firm, yellowish white nodule measuring 2 by 1 by 1 cm. On cross section, it was homogenous and sharply demarcated from the surrounding tissue.

DR. ROBERT A. MOORE: Quite aside from answering some of the specific questions raised in the clinical discussion, such as the cause of the pericardial effusion, the essential task of the pathologist in analyzing this case is to determine the primary site of the tumor. Manifestly, there was a tumor in the lung and about the right hilus which exhibited many of the characteristics of a primary carcinoma of the bronchus or lung. Certainly, from the standpoint of gross appearance, it might have been either one of two types of carcinoma; that is, a bronchogenic carcinoma or one of the so-called peripheral lung tumors. The latter are characterized by depressed, radiating surface scars, the tumor lying just beneath the scar. An interesting question concerning the origin of such tumors arises, for when one has seen several of them he is not at all convinced that the tumor can produce as much scarring and retraction of the pleura as is characteristically seen; hence the possibility that a peripheral lung tumor originates in a pre-existing scar must be considered.

Turning to the prostate gland, the gross appearance of the nodule in that structure also bore the characteristics of a primary tumor. It was located in the posterior lobe of the gland, was unilateral, and was of a size consistent with many occult carcinomas of the prostate. Our major problem, then, was to determine whether this man had two

primary tumors, or whether he had one tumor which metastasized to several other organs. If one assumes that there was a single primary tumor which arose in the lung, could the nodule in the prostate have represented a metastasis? Such an explanation is most unlikely for metastatic carcinoma of the prostate is practically unknown. Occasionally metastases of the prostate are seen when the organ is invaded by tumors arising in nearby structures; that is, the rectum, the bladder or from reflections of the peritoneum. But an actual carcinoma nodule in the prostate, metastatic from a distant organ is an extreme rarity, almost as rare as primary carcinoma of the seminal vesicles of which, I believe, there are some seven or nine cases in the world literature. I have read all of those reports and on the basis of the description given have my doubts as to whether any actually were primary in the seminal vesicle. The converse explanation, that is, that the tumor was primary in the prostate and metastasized to the lung, liver and kidney must also be considered. In order to attempt to reach a final conclusion, we must rely on the microscopic sections and examine the histologic structure and the appearance of the lesions.

The first section (Fig. 2) is from a bronchus surrounded by tumor. The mucosa is in large part replaced by tumor; there are a few islands of normal glands remaining. The tumor lies outside the muscularis; as Dr. Johnson pointed out in the gross description, no ulceration of the mucosa could be detected and in those sections which have been examined microscopically, the epithelium of the surface is intact. Now that observation has an important bearing on our final conclusion, particularly if it holds for all of the mucosal surface. Carcinoma of the bronchus originates from surface epithelium rather than from the glands themselves; and if intact surface epithelium exists over the entire extent of the tumor nodule in the lung, a serious doubt would arise that the tumor represented a primary carcinoma of the bronchus, at least of the type usually seen.

There are certain organs in the body that give rise to tumors which produce mucin; such tumors arise from cells which themselves are capable of producing mucin. There are certain other organs whose cells do not possess this characteristic. We are fortunate here in dealing with bronchus and prostate. Mucinous carcinoma of the prostate does not exist because the prostatic epithelial cell does not have the capacity, under any circumstance, to make mucin. On the other hand, primary carcinoma of the bronchus is frequently of the mucinous type, though not exclusively so. Adenocarcinoma of the lung, the type seen here, occasionally does not produce mucin. Mucicarmine stains demonstrate that the tumor cells are free of any intracellular mucin. The cell itself is of a type consistent with an origin either in the bronchus or prostate; there is nothing in the histologic appearance which points to one or the other with any certainty. If, as are 35 to 40 per cent of all primary malignancies of the lung, this tumor were an epidermoid carcinoma, the problem would be simple for an epidermoid carcinoma of the prostate is an extreme rarity. I believe there are forty or fifty cases reported in the literature; perhaps all of these arise from the prostatic utricle and not from the prostate itself. They are relatively benign and metastasize late.

In the next section (Fig. 3), lung, pleura and a mediastinal node are shown; the tumor has invaded both the node and the pleura and has obliterated the pleural cavity on the medial side of the lung. In Figure 4, the periphery of the lung is seen; the section represents an excellent example of lymphatic invasion in the pleura by adenocarcinoma. The tumor exhibits a moderately anaplastic character in that

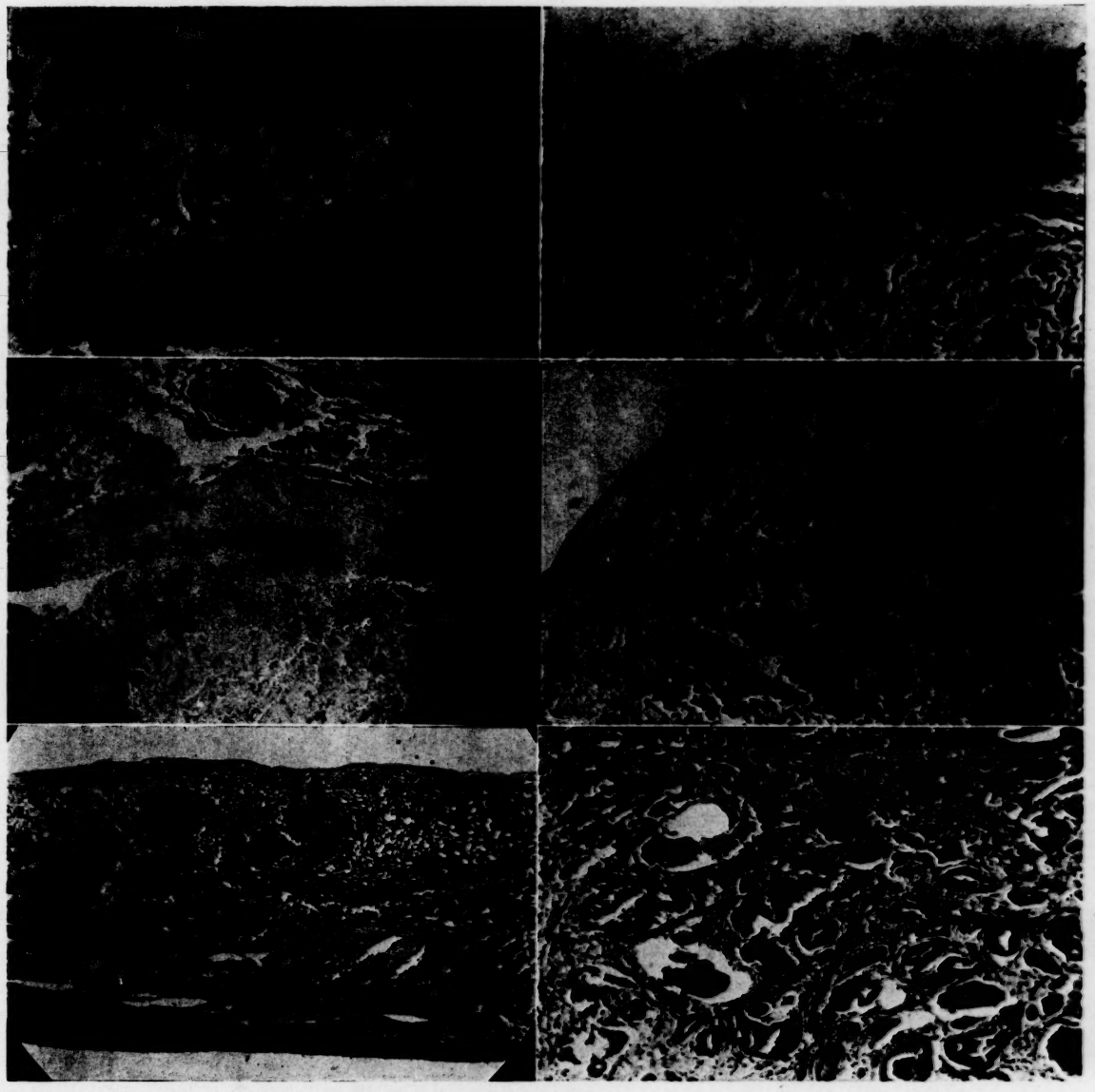


FIG. 1. Section of cell block made from pleural fluid. Note the tendency toward acinar formation.
FIG. 2. Section showing a bronchus surrounded by tumor.
FIG. 3. Section showing the lung, pleura, and a mediastinal node involved by tumor.
FIG. 4. Lymphatic invasion by adenocarcinoma in the pleura.
FIG. 5. Section showing invasion of the pericardium by tumor.
FIG. 6. Section of the primary carcinoma in the prostate. Note that many of the glands have pulled away from the basement membrane.

there is a slight to moderate amount of connective tissue in between the tumor cells. Figure 5 shows a section of the pericardium and pleura. The tumor has invaded the pericardium and the invasion is certainly an adequate explanation of the origin of the pericardial effusion. When the pericardium is invaded by tumor there may be a variable amount of fluid in the pericardial sac. In this instance, you remember 1,300 cc. were found.

Finally, the section of the prostatic nodule (Fig. 6) could not be a more typical example of primary carcinoma of the prostate. The tumor is composed of acini of variable size and structure. They are composed largely

of basophilic cells and there is little evidence of secretion. The connective tissue of the stroma of the prostate is not greatly altered. A point that is extremely valuable, but not diagnostic because it is an artefact, is that many of the glands are pulled away from the basement membrane. This feature is highly characteristic of carcinoma of the prostate. I lay great weight on the presence of this artefact in making a microscopic diagnosis of carcinoma of the prostate. In some way the epithelial cells of a carcinoma of the prostate respond differently than other cells to the agents used in the preparation of microscopic sections; that is, to formaldehyde, to dehydration in alcohol and to heating. This phenomenon is not seen when celloidin sections of carcinoma of the prostate are prepared.

To return to the question of the origin of the primary tumor in this case, we must accept the carcinoma of the prostate as being primary. The tumor exhibits all of the characteristic gross and microscopic findings. It is well known that primary carcinoma of the prostate may be occult and yet may give rise to metastases which, in size, extent and in production of clinical symptoms, may be all out of proportion to the size and extent of the primary tumor. There is a generally accepted dictum which we have pointed out at these conferences previously, namely, that in attempting to establish whether in a given case there is one or two tumors, the burden of proof is on the individual who says there are two tumors. We can muster few positive facts to support the concept that there was a primary carcinoma of the bronchus. We conclude, therefore, that the patient had a primary carcinoma of the prostate with metastases to the lung, hilar lymph nodes, pleura of the right lung, mediastinum, pericardium, liver and right kidney.

One point concerning the metastases should be made. From time to time, we have suggested the value, in differential diagnosis, of the location of metastases. This patient had metastases to the liver and the right kidney which would be more characteristic of carcinoma of the bronchus than of carcinoma of the prostate. As I have also pointed out before, however, all deductions based on differences in the distribution of metastases of carcinoma of the lung in contrast with other carcinomas are non-operative as soon as the latter metastasize to the lung, for then secondary metastases may arise in the same distribution as those from a primary carcinoma of the bronchus. The primary tumor in this case, therefore, despite the fact that it arose in the prostate, having gone to the lung, may then have metastasized further to any other organ.

In regard to the heart, it weighed 420 Gm. The patient weighed 97 Kg. and it would be difficult to establish a diagnosis of hypertrophy of the heart in view of the total body weight. Perhaps there was slight cardiac enlargement but it was certainly not striking. Considering the question of the presence or absence of cardiac failure, we observed at autopsy slight edema of the extremities and chronic passive congestion of the liver and spleen; these findings could not be accounted for on the basis of the right hydrothorax. We would, therefore, conclude that the patient had an element of congestive failure and that presumably it was caused by the accumulation of 1,300 cc. of fluid in the pericardial sac. He had only slight arteriosclerosis of the coronary arteries and there was no evidence in the myocardium that he had suffered coronary insufficiency. Finally, as to the presence of red blood cells in the urine, we suspect that that finding was of no significance except to make the clinicians' problem more difficult, for in our examination to explain the hematuria the only finding, either grossly or microscopically, were a few petechiae in the medulla of the kidney. Why they were there,

I do not know, unless they can be explained on the basis of cardiac failure.

DR. ALEXANDER: Dr. Moore, because of your very extensive experience with carcinoma of the prostate, I should like to ask, first, the incidence of involvement of the lung by carcinoma of the prostate, and secondly, whether you would consider unilateral involvement of the lung unusual?

DR. MOORE: It is unusual, Dr. Alexander, for carcinoma of the prostate to produce the type of metastasis such as you saw here, that is, a mass in the mid-zone of the lung extending into the mediastinum. We have mentioned on occasion that one basis for distinguishing a primary carcinoma of the lung from other tumors is the occurrence of metastases to a regional node. At a reasonably early stage in the disease, metastatic carcinoma arising in other organs will appear in the lung but not in the regional node, while at the same stage the primary tumor of the bronchus will have metastasized to the regional node. The metastasis seen here is unusual for a tumor having arisen elsewhere and I cannot, therefore, absolutely deny that this man did not have two tumors, one of which was in the bronchus. However, I can marshall no objective positive evidence to support such a concept and, therefore, on the thesis that the burden of proof is on the pathologist who says there are two tumors, we concluded that there was only one.

Anatomic Diagnoses: Carcinoma of the prostate; metastatic carcinoma involving the lung, hilar lymph nodes, pleura of right lung, mediastinum, pericardium, liver, and right kidney; hydrohemopericardium (1,300 cc.); hydrohemothorax, right (300 cc.); infarct of upper lobe of right lung; chronic passive congestion of liver and spleen.

Case Report

Destructive Osseous Lesions in Early Syphilis*

Response Following Penicillin Therapy

ROBERT J. GLASER, M.D. *and* VIRGIL SCOTT, M.D.
ST. LOUIS, MISSOURI

DESTRUCTIVE lesions of the bones are a well authenticated but rare type of osseous involvement in early syphilis. Although other skeletal manifestations are not uncommon during this stage of the disease, Reynolds and Wasserman[1] were able to collect only fifteen cases of destructive bone lesions from the literature, prior to 1942. These authors reported an additional fifteen cases observed in a total of approximately 10,000 patients with early syphilis. Since their report Exley and Newton[2] and Lefkovits and Cross[3] have each presented one case.

The favorable response of this type of lesion during weekly treatment with the arsenicals and bismuth has been demonstrated.[1] Under prolonged treatment methods, complete healing as determined by x-ray examination has occurred in periods ranging from four to ten months and in the few patients on whom follow-up data are available, the ultimate prognosis for cure with rare exceptions appears to be no less favorable than in the absence of this complication. With the demonstration of the therapeutic efficacy of penicillin in uncomplicated early syphilis, it becomes of importance to determine the effect of this antibiotic on rare manifestations of the disease such as this, and in addition, since it has not previously been studied, the effectiveness of an intensive regimen, wherein treatment is completed even before roentgenographic evidence of bone repair has begun.*

Penicillin has been employed in only one published case, that of Lefkovits and Cross.[3] Although in their patient the initial response was satisfactory, the effect of treatment was complicated by the administration of two courses of penicillin (2.4 million units in 7.5 days, 4.0 million units in ten days) separated by an interval of approximately one month. Parenthetically, the indication for retreatment is not stated in the protocol. Since their patient was observed for only forty-eight days following the initial course of penicillin and healing was not complete at that time, the ultimate outcome was not determined.

CASE REPORT

N. P., (No. 129,849), a twenty-three year old white divorced female, reported to the Washington University Clinics on October 17, 1945, complaining of severe headache of six weeks' duration. On examination in the Otolaryn-

* No reports have appeared regarding the effectiveness of intensive arsenotherapy on this type of lesion.

* From the Departments of Internal Medicine and Preventive Medicine, Washington University School of Medicine, the Syphilis Clinic of the Washington University Clinics and the Barnes Hospital, St. Louis, Mo. The work described in this report was performed under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Washington University, and under a grant-in-aid from the National Institute of Health, United States Public Health Service.

gology Clinic, acute frontal sinusitis was suspected but was not confirmed by x-ray. Because the serologic test for syphilis was positive on routine examination, she was referred to the Syphilis Clinic at which time the diagnosis of early syphilis was established. The patient was admitted to the Barnes Hospital on November 8, 1945.

According to the patient serologic tests for syphilis had been negative on three previous occasions: ten years before her present admission, while hospitalized elsewhere for an appendectomy; one year before on premarital examination and four and one-half months previously on pre-employment testing. At the time of her marriage in October, 1944, her husband's premarital STS* was said also to have been negative. The marriage lasted six months; the patient obtained a divorce in March, 1945, nine months before her admission to the hospital. The husband's syphilitic status at the time of separation is not known, but the patient's allegedly negative STS four months later is presumptive evidence that he was not infected.

During the five months prior to entry the patient admitted repeated sexual exposure with a single consort. Two and one-half months before admission the latter developed a urethral discharge and was treated for gonorrhea elsewhere with penicillin.† At the same time the patient also received penicillin (three injections in one day), the diagnosis of a gonococcal infection apparently based on epidemiologic evidence.

Shortly prior to this time (about three and one-half months before admission) the patient struck her head in the left occipitoparietal region on a sharp ledge. A tender "knot" developed at the site; the lump persisted although tenderness disappeared in three days. After a symptom-free interlude of approximately six weeks, headaches characteristic of the present illness began two months before admission. These were predominately frontal in location, dull but intense and worse on movement of the head; at times there was radiation posteriorly over the cranial vault. The characteristic feature of the headache was its nocturnal occurrence, the patient being awakened regularly at 4:00 A.M. At one time her right eyelid was said to have been swollen and discolored but these signs subsided spontaneously and were not apparent on admission. Approximately six weeks before admission the headache became bilateral and point tenderness developed on the left at the site of the previous injury. Simultaneously, three scattered skin lesions appeared. The patient denied any lesion, genital or extragenital, which in retrospect might have represented a chancre. There had been no bubo, generalized skin rash, oral lesions, sore throat or other bone pain.

On physical examination after admission to the hospital, the rectal temperature was 38.0°C., pulse 100 per minute, respirations 20 per minute, blood pressure 130 mm. Hg systolic and 70 diastolic. Three red, partially crusted papules were present on the skin; one each on the inner surface of the left arm, the right side of the neck and the medial aspect of the left mid-thigh. Over the region of the left occipitoparietal junction a small, exquisitely tender, hard mass measuring 1 by 2 cm. was easily palpable. This seemed attached to the skull but not to the overlying skin. No alopecia was evident and no other areas of tenderness or tumefaction were discovered, either over the skull or over the long bones. Examination of the eyes was not remarkable except for slight hyperemia of the optic discs. No lesions were visible on the mucous membranes of the oropharynx. The remainder of the physical examination was within normal limits. No adenopathy (regional or general) was present, no lesions or scars were visible on the external genitalia and the cervix appeared normal on inspection. The neck was not stiff and the neurologic examination was entirely negative.

Laboratory studies included a normal red blood cell count and hemoglobin. The leukocytes numbered 11,100; the differential showed 1 per cent juveniles, 4 per cent stabs, 52 per cent segmented forms and 43 per cent lymphocytes. The urinalysis was normal. On dark field examination of serum expressed from the papule

* Serologic test for syphilis.

† From the standpoint of syphilis this contact remained clinically and serologically negative on repeated examinations over a seven months period (November, 1945 to June, 1946).

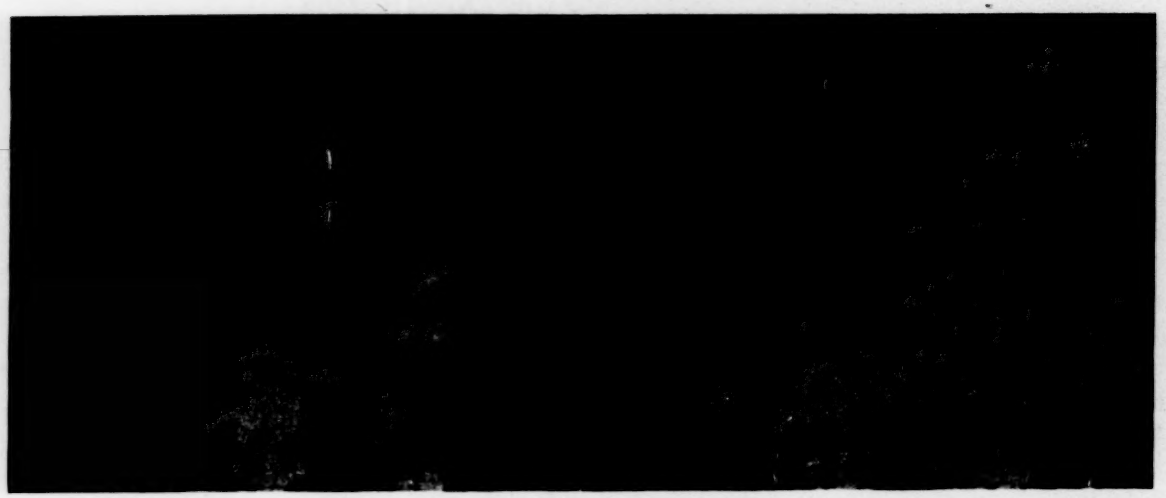


FIG. 1. Lateral roentgenogram of skull before treatment. Three areas of bone destruction are visible in the parietal bone. A similar lesion is present in the frontal bone.

FIG. 2. Lesions show evidence of healing eighty-nine days following completion of penicillin therapy.

on the left arm, numerous Treponema pallidum were seen. Quantitative blood STS was reported as 120 Kahn units. Examination of the cerebrospinal fluid showed 15 lymphocytes, total protein 39 mg. per cent, colloidal test 0000000000 and a negative Kolmer complement fixation reaction with 0.5 cc. of spinal fluid. An ophthalmologic consultant recorded normal visual acuity and fields. The x-ray film of the skull showing multiple areas of destruction is reproduced in Figure 1. No abnormalities of the thoracic cage were evident on roentgenogram of the chest.

Hospital Course. Antisyphilitic treatment consisted of commercial sodium penicillin administered by intramuscular injection in divided doses of 50,000 units every two hours day and night for ninety-six injections, a total of 4.8 million units in 7.5 days. No Herxheimer reaction (clinical or febrile) followed the institution of treatment. Within forty-eight hours bone pain and tenderness were strikingly improved and by the fifth day of treatment they had disappeared completely. The skin lesions healed rapidly. At the completion of treatment the quantitative blood STS was unchanged (120 KU); the cerebrospinal fluid contained two cells and was normal in other respects.

Follow-up Observations. Clinical and quantitative serologic examinations have been per-

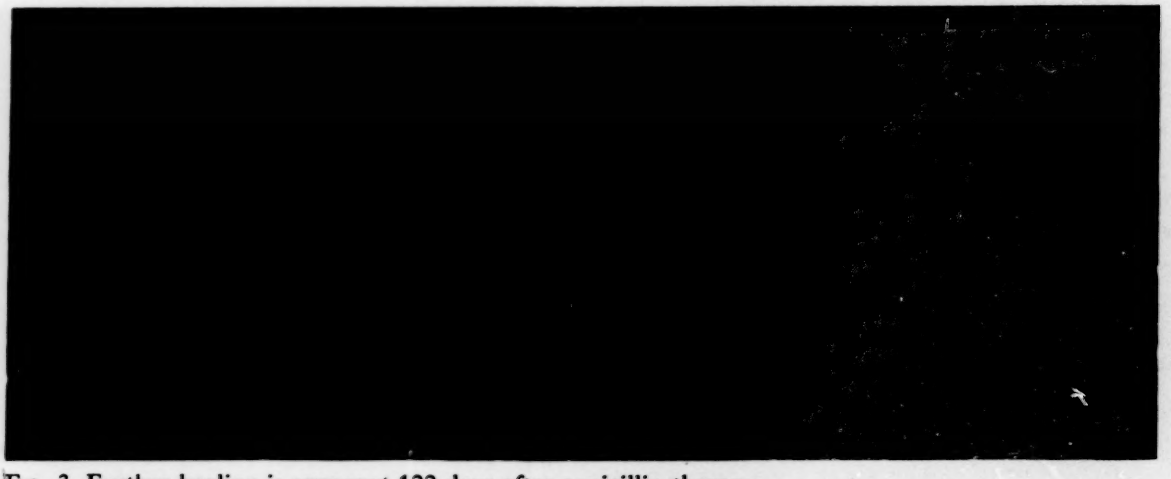


FIG. 3. Further healing is apparent 122 days after penicillin therapy.

FIG. 4. Lesions are completely healed on the two-hundred eighth post-treatment day.

formed at approximately monthly intervals during the first post-treatment year and every three months thereafter. No recurrent infectious mucocutaneous lesions have been observed; the patient has remained symptomatically well during the one year and four months since treatment. Quantitative blood serologic tests for syphilis in relation to days after the termination of penicillin therapy are shown in Table I. The cerebrospinal fluid on re-examination nine months following treatment was normal.

TABLE I
SEROLOGIC RESPONSE FOLLOWING PENICILLIN THERAPY

Days After Treatment	Titer (Kahn Units)
1	120
29	40
50	4
64	4
70	3
92	4
120	2
166	2
215	0
236	1
271	1
295	1
341	1
474	0

Periodic roentgenograms have been obtained since the completion of penicillin therapy. On the twenty-fourth post-treatment day there was as yet no change in the appearance of the lesions. As shown in Figure 2, evidence of healing had become apparent by the eighty-ninth day and at the end of 122 days (Fig. 3) there had been progressive improvement. On the next film (208 days) no residua of the destructive lesions remained. (Fig. 4.) The most recent x-ray examination of the skull, made 465 days after the completion of treatment, appeared normal.

COMMENTS

Although destructive osseous lesions are rare in early syphilis, other evidences of skeletal involvement (arthralgia, osteocopic pain and proliferative periostitis) are exceedingly common. For example, Wile and Senear[4] in a painstaking clinical study of 165 patients with early syphilis found symptoms and/or signs referable to the bones and joints in sixty patients (36 per cent). The frequency of destructive lesions is not known since no one has reported the results of complete roentgenologic study on a series of patients with early syphilis. From the available reports, the sites of predilection appear to be the skull, the bones about the sternoclavicular joint and the long bones, in that order.

The diagnostic problem presented by these lesions has been repeatedly stressed[1,3,5] and is re-emphasized by our own patient who in the six weeks prior to admission consulted three physicians and was accorded three different diagnoses—"sinusitis," "neuralgia" and "menopausal syndrome." It was only after an additional three weeks and six clinic visits to our own institution that the correct diagnosis was suspected and then only after the admission STS, routinely performed on all new patients, was reported positive.

In this patient the therapeutic response following penicillin therapy appears to have been as prompt as has been recorded during prolonged treatment with metal chemotherapeutic agents. Symptomatic relief occurred within forty-eight hours, striking and progressive improvement was apparent on follow-up x-ray examinations on the eighty-ninth and 122nd post-treatment days and all roentgenographic evidence of the lesions had disappeared before the 208th day (approximately seven months). The schedule employed in this patient (4.8 million units in 7.5 days) was one of the penicillin regimens assigned to this institution* for the routine treatment of patients with early syphilis. No additional penicillin was administered because of the presence of destructive bone involvement.

Although the relationship of the preceding blow on the head to the subsequent

* By the Penicillin Panel of the Subcommittee on Venereal Diseases, National Research Council, the agency administrating the nationwide cooperative study of penicillin in syphilis.

development of destructive lesions of the skull is conjectural, it is pertinent that Chesney, Turner and Halley[6] have demonstrated the predisposing influence of trauma on cutaneous lesions of experimental syphilis in rabbits and have reported similar instances in early syphilis in man. Parenthetically, in late syphilis trauma is more frequently implicated as a factor predisposing to the development of lesions, osseous as well as cutaneous, e.g., in benign late (gummatous) syphilis.[7]

Whether the penicillin administered elsewhere shortly before onset of the present illness affected the course of syphilis in this patient is speculative. There is ample evidence both in man and in the experimental animal that penicillin in small doses administered during the incubation period of syphilis may modify or completely suppress the early manifestations of the disease.[8,9] Although it was not possible to date the onset of syphilitic infection in this patient either by historical data or by epidemiologic investigation, it is conceivable that the small amount of penicillin administered for gonorrhea approximately two weeks before the onset of headache and four weeks before the appearance of three scattered skin lesions of the secondary type may have exerted a modifying and/or suppressing effect.

SUMMARY

A case report of destructive osseous lesions of the skull in early syphilis is presented. Penicillin therapy (4.8 million units in 7.5 days) afforded prompt symptomatic relief and complete healing of the involved areas within a seven month period. The results in this patient compare favorably with those reported during prolonged treatment with the arsenicals and bismuth.

REFERENCES

1. Reynolds, F. W. and Wasserman, H. Destructive osseous lesions in early syphilis. *Arch. Int. Med.*, 69: 263, 1942.
2. Exley, M. and Newton, A. W. Osseous syphilis. Report of a case. *New England J. Med.*, 234: 661, 1946.
3. Lefkovits, A. M. and Cross, K. R. Bone lesions in early syphilis. Report of a case. *Am. J. Clin. Path.*, 16: 693, 1946.
4. Wile, U. J. and Senear, F. E. A study of the involvement of the bones and joints in early syphilis. *Am. J. M. Sc.*, 152: 689, 1916.
5. Wile, U. J. and Welton, D. G. Early syphilitic osteomyelitis with a report of two cases. *Am. J. Syph., Gonor. & Ven. Dis.*, 24: 1, 1940.
6. Chesney, A. M., Turner, T. B. and Halley, C. R. L. Studies in experimental syphilis. VIII. On the localization of syphilitic lesions in inflamed areas. *Bull. Johns Hopkins Hosp.*, 42: 319, 1928.
7. Moore, J. E. The Modern Treatment of Syphilis. 2nd ed., p. 8. Springfield, Ill., 1944. Charles C. Thomas.
8. Leifer, W. and Martin, S. P. Effect of penicillin on course of early syphilis. *J. A. M. A.*, 130: 202, 1946.
9. Magnuson, H. J. and Eagle, H. The retardation and suppression of experimental early syphilis by small doses of penicillin comparable to those used in the treatment of gonorrhea. *Am. J. Syph., Gonor. & Ven. Dis.*, 29: 587, 1945.

SOUTHERN SOCIETY FOR CLINICAL RESEARCH

FIRST ANNUAL MEETING, NEW ORLEANS, JANUARY, 1947

Officers for 1947–1948

President
TINSLEY R. HARRISON, M.D.
Dallas, Texas

Vice-president
WILLIAM J. DARBY, JR., M.D.
Nashville, Tenn.

Secretary-Treasurer
THOMAS FINDLEY, M.D.
New Orleans, La.

Councillor for Three Years
J. W. BEARD, M.D.
Durham, N. C.

Councillor for Two Years
PAUL B. BEESON, M.D.
Atlanta, Ga.

Councillors for One Year
ROBERT M. MOORE, M.D.
Galveston, Texas
HAROLD D. GREEN, M.D.
Winston-Salem, N. C.

This Society was organized in the fall of 1946 by a representative group from various schools in the South who believe that enough good work is now being done below the Mason-Dixon Line to justify a regional organization.

The object of the Society is the encouragement of research in the various medical sciences and the establishment of a forum from which new ideas may be presented to the medical profession at large.

The geographical limits of this Society conform with those of the Southern Medical Association. The first annual meeting was held in New Orleans on January 25, 1947.

Office of the Secretary
Ochsner Clinic
New Orleans 15, La.

Experimental Observations on the Production of Pericardial Adhesions and on Ligation of Coronary Arteries in Rats

Alex W. Boone, M.D. (*introduced by Joseph W. Beard, M.D.*)

From the Department of Surgery, Duke University School of Medicine, Durham, N. C.

Claude S. Beck and others have pioneered work indicating that temporary augmentation of the coronary circulation is possible by producing adhesions between the myocardium and pericardium. As yet, however, no satisfactory simple method of producing these adhesions has been evolved.

Experiments have been performed upon 227 rats to determine the efficiency of substances that might be injected into the pericardial sac and thereby furnish collateral extracoronary blood supply. Experiments have also been performed to determine the effect of adhesions upon the relative physical efficiency of the normal rat and of the rat subjected to ligation of the left coronary artery. Various concentrations of thirteen different detergents and six miscellaneous agents were placed in the pericardial sac of the rat. Five per cent monoethanolamine oleate proved to be the most efficacious and nontoxic of the agents tried, producing good vascular adhesions without complications. These adhesions did not affect the efficiency of normal rats. Ligation of the left coronary artery of normal rats diminished their physical efficiency. Production of adhesions soon after ligation of the left coronary artery had little beneficial effect.

Experimental Aortic Valvulotomy

H. G. Smithy, M.D. *and* Edward F. Parker, M.D. (*introduced by William J. Darby, M.D.*)

From the Department of Surgery, Medical College of the State of South Carolina, Charleston, S. C.

In an effort to perfect a technical approach to the aortic valve, a series of dogs was studied with the view of developing a surgical procedure which might be applicable to young patients suffering from aortic stenosis.

The aortic valve has been successfully divided by a specially devised valvulotome which is passed into one of the aortic cusps through the wall of the ascending aorta with the resultant production of aortic insufficiency. Technically, the procedure is complicated by hemorrhage from the aortic wound. Methods utilized in controlling the bleeding and in the production of the valvular lesion are discussed. Further studies are in progress relating to electrocardiographic changes, microscopic alterations of the aorta and the permanency of the valvular lesion.

Mechanism of Edema Formation in Thyrotoxic Heart Disease

Arthur J. Merrill, M.D. *and* (*by invitation*) Walter H. Cargill, M.D.

From the Department of Medicine, Emory University School of Medicine, Atlanta, Ga.

We have previously presented evidence for a forward failure hypothesis of edema formation in congestive heart failure. Essentially this consists of a marked reduction in renal plasma flow, and filtration rate is independent of venous pressure levels and is closely related to inadequacy of cardiac output. The low filtration rate results in a reduction of the amount of salt and water presented to the tubules. Almost complete reabsorption by the tubules occurs with a net retention of salt and water and consequent edema formation. The cause of cardiac edema in patients with high cardiac outputs, as in thyrotoxicosis, has not been explained.

In thyrotoxicosis the cardiac output and basal metabolism rate were elevated concomitantly but the cardiac output was slightly higher after the patient became compensated than it was during severe failure.

The renal plasma flow in uncomplicated thyrotoxicosis followed no definite pattern but in the same patient tended to fall as the basal metabolism fell.

In seven patients with edema and orthopnea which were controlled easily, the renal plasma flow and filtration rate were normal or elevated. In all with a slightly diminished renal plasma flow, a supernormal level was found shortly after the patient became compensated. In one patient with moderate failure the renal plasma flow was decreased. In one patient with the most severe anasarca and ascites the renal plasma flow and filtration rate were quite low.

As the patient's thyrotoxicosis improved with propylthiouracil, first the filtration rate and finally the renal plasma flow became normal but the renal plasma flow was decreased. The latter increased as the patient's thyrotoxicosis improved with propylthiouracil.

Thus further evidence is found of a mechanism for reduction of the renal plasma flow and filtration rate when the cardiac output becomes inadequate for the metabolic needs of the tissues, even though the cardiac output may be well above the accepted average normal. When this vasoconstriction is extreme, the filtration rate and consequently salt and water filtration are reduced and edema occurs. One may surmise that the patients with less severe failure and normal renal studies at rest had inadequate cardiac outputs on exertion. We have shown that this will produce depression of the renal plasma flow and filtration rate in other types of heart failure and it is logical to suppose that a similar mechanism would operate here.

Changes in Respiratory Efficiency and Dynamics in Experimental Pulmonary Congestion

Howard E. Heyer, M.D., James Holman, M.D. *and* George T. Shires, M.D. (*introduced by Morton F. Mason, M.D.*)

From the Department of Medicine, Southwestern Medical College, Dallas, Tex.

Experimental pulmonary congestion and edema were produced in dogs by rapid venous infusion of saline and buffer solutions. Continuous determinations were made of tidal exchange, intrapleural pressure fluctuations, ventilation per minute and of jugular venous pressure. Eighteen animals were utilized in all. In several experiments comparative determinations were made at rest (nembutal anesthesia) as well as after the hyperpnea induced by rebreathing CO_2 and oxygen, or by experimental congestion. The rapid infusion produced marked pulmonary congestion and edema, confirmed by postmortem examination. Generalized visceral congestion and progressive elevation of venous pressure to over 500 mm. of saline were noted in all experiments. Intrapleural pressures were below atmospheric levels prior to infusion, but with increasing congestion expiratory pressures rose well above atmospheric levels in all cases. Inspiratory pressures either became more negative or shifted slightly toward atmospheric levels. Total intrapleural pressure changes increased markedly and mean intrapleural pressures deviated toward atmospheric levels. Carbon dioxide hyperpnea caused marked increases in total intrapleural pressure changes and an increase in the negative pressure developed during inspiration. In five of eight animals given CO_2, the expiratory intrapleural pressure remained below the atmospheric level, even with marked hyperpnea; in the remaining three animals it rose above this level.

The average tidal air increased markedly after CO_2 administration (often doubling), and the ventilation per minute rose even more sharply. During maximum pulmonary congestion tidal exchange decreased markedly, even with gross hyperpnea, while the ventilation was either slightly increased or decreased.

$$\frac{\text{Tidal exchange (cm.}^3\text{/meter}^2)}{\text{Total intrapleural presssure change}}$$

was utilized as an index of efficiency of respiration. This index rose abruptly after CO_2 administration and decreased sharply after pulmonary congestion was produced. Vagotomy slowed the respiratory rate, but did not abolish the shift in intrapleural pressure to levels above atmospheric, nor did it prevent the rapid decline in respiratory efficiency after congestion. Marked activity of expiratory muscle groups occurred with severe pulmonary congestion. Section of the cervical cord abolished these movements, but failed to cause expiratory intrapleural pressures to drop to subatmospheric levels in all cases. The authors conclude that hyperpnea produces increased efficiency of breathing in the normal lung, whereas the hyperpnea of pulmonary congestion is accompanied by a marked decrease in efficiency of respiration. The latter phenomenon is ascribed mainly to changes in the distensibility of pulmonary tissues. The shift in intrapleural pressure toward positive values (with congestion) is partially explainable by increased activity of expiratory muscles, but the failure of vagotomy and cord section to abolish these changes indicates that local changes in the lungs are also causative.

Pulmonary Arterial Pressures in Congestive Failure and Emphysema

John B. Hickam, M.D. *and* Walter H. Cargill, M.D. (*introduced by Eugene A. Stead, Jr., M.D.*)

From the Duke University School of Medicine, Durham, N. C.

Many phenomena seen in diseases of the heart and lungs are commonly ascribed to elevation of pressure in the lesser circulation. Until recently, there have been few opportunities for determination of this pressure in man. The technic of intracardiac catheterization permits measurement of pressures within the pulmonary artery and simultaneous determination of the cardiac output by the Fick method. This technic has been applied to the study of the pulmonary circulation in patients with pulmonary emphysema, congestive heart failure, and mitral stenosis, conditions which have been thought to bring about an elevation of pressure in the lesser circulation.

Pulmonary arterial pressure and cardiac output were determined while subjects were at rest and while they were carrying out exercise sufficient approximately to double the resting oxygen consumption. In normal subjects the mean pulmonary arterial pressure at rest is of the order of 10 to 15 mm. of mercury and is substantially unchanged by increases in cardiac output up to nearly twice the resting level. Subjects with emphysema who have an elevated pulmonary pressure at rest show a further large increase in pressure when the cardiac output is raised by exercise. Subjects with congestive failure on the basis of hypertension or aortic regurgitation usually have a high resting pulmonary pressure. During exercise, the pulmonary pressure undergoes an additional large elevation, but the cardiac output is increased little or not at all. The results in subjects with advanced mitral stenosis resembled those seen in left ventricular failure.

The data indicate that the normal pulmonary vascular bed can accommodate considerable increase in blood flow over the resting level without a significant increase in pulmonary arterial pressure. The results in emphysema suggest a rigid vascular bed which responds with a sharp elevation of arterial pressure to an increase in cardiac output. The mechanism by which the pulmonary pressure becomes elevated in cases of left ventricular failure is uncertain. It might possibly result from elevation of the left atrial pressure, constriction of pulmonary arterioles or development of edema within the lung. In mitral stenosis the failure of the cardiac output to rise in correspondence with the elevation of pulmonary pressure during exercise was unexpected.

Use of Tetraethylammonium Chloride in the Treatment of Experimental Acute Arterial Insufficiency

F. W. Cooper, Jr., M.D. (*introduced by Arthur J. Merrill, M.D.*)

From the Department of Medicine, Emory University School of Medicine, Atlanta, Ga.

It has been proved conclusively by Leriche and his co-workers that sympathectomy will prevent massive gangrene and death following extensive arterial resections in animals. "The critical period" following arterial resection appears to be the optimal time for removal of constrictive arterial impulses which may inhibit the dilatation of collateral vessels.

A group of twenty animals weighing 9 to 15 Kg. was operated upon with the trifurcation of the aorta being excised distal to the inferior mesenteric artery. The deep circumflex iliac arteries, the two external iliac arteries and the common hypogastric trunk were excised. Ten of the animals were given tetraethylammonium chloride in the proportion of 25 mg. per Kg. of body weight as a sterile 10 per cent solution, intramuscularly. Similar doses were given every eight to twelve hours for three days.

In the control group nine of the animals died within one to five days with paralysis, discoloration and swelling of the posterior extremities. All of the animals treated with tetraethylammonium chloride survived except for one in which extensive cellulitis developed following injection of the drug through technical error in the posterior extremities. The animals so treated demonstrated a transient weakness and decreased functional tolerance for one to four days but returned to relatively normal activity at the end of this time.

The enlargement of the collateral channels about the site of aortic excision was demon-

strated by arteriography. Tetraethylammonium chloride may be a valuable adjunct in the treatment of acute arterial injuries.

Phlebography for the Study of Obstruction of the Veins of the Superior Vena Caval System

Sol Katz, M.D., Hugh Hudson Hussey, M.D. *and* James Ross Veal, M.D. (*introduced by Harold Jeghers, M.D.*)

From the Departments of Medicine and Surgery, Georgetown University School of Medicine, Georgetown Division of Medical and Surgical Division of Gallinger Municipal Hospital, Washington, D. C.

Phlebography is a precise method for study of lesions causing obstruction of the superior vena cava or its main tributaries, except the internal jugular vein which is inaccessible. Diodrast has usually been employed as the contrast medium. The external jugular vein is the preferred site of injection for visualization of obstruction of the superior vena cava or innominate vein; the median basilic vein, for the subclavian and axillary veins. The interpretation of phlebograms of the superior vena caval system is simple and errors are much less frequent than with phlebograms of the lower extremity. No other method, except anatomic dissection, affords as much information about the location and extent of collateral venous circulation.

Cases illustrative of obstruction of the superior vena caval system at various points are presented. It is emphasized that comparative measurements of the venous pressure are a valuable supplement to phlebography. They vrovide a more exact appraisal of the functional capacity of the collateral circulation than phlebographic study alone.

Relation between Arterial Pressure and Blood Flow in the Foot

P. Scheinberg, M.D., E. W. Dennis, M.D., R. V. Robertson, M.D. (*by invitation*) *and* Eugene A. Stead, Jr., M.D.

From the Departments of Medicine, Emory University, Atlanta, Ga., and Duke University School of Medicine, Durham, N. C.

The relationships between blood flow and arterial pressure in man have never been clearly elucidated. A satisfactory technic for raising and lowering the arterial pressure in a part without using either vasoconstrictor drugs or intense sympathetic stimulation or causing venous congestion has been lacking. Because of its relatively large surface area, the foot offers an ideal for studying the relation between arterial pressure and blood flow in the skin. By standing upright the mean arterial pressure in the foot may be doubled. Venous congestion can be avoided by applying to the foot a pressure which exceeds the hydrostatic venous pressure but is well below the arterial diastolic pressure. On release of the external pressure, blood flows into the foot under a tremendous pressure head, which is unopposed on the venous side until the foot is filled. This seems to be a logical means of increasing the rate and amount of blood flowing into a foot with vascular disease; contrary to most current clinical procedures, it does not produce a deficit of blood flow for each gain, for the pressure required to empty the foot of its venous blood does not impede arterial inflow. The blood flow with the subject in the recumbent and standing positions is measured by means of a plethysmograph.

In a given subject the blood flow in the foot is related to: (1) Peripheral vascular resistance, which depends on (*a*) the amount of vasodilatation, (*b*) the amount of blood in the vessels which must be moved forward, and (2) the arterial pressure head. With the subject recumbent the blood flow in the foot is greatest when the foot is emptied of its venous blood and the vessels are maximally dilated by heat or previous arterial occlusion, for this situation offers the least peripheral vascular resistance. On standing, the blood flow is also greatest when the foot has previously been emptied of its venous blood.

On standing the mean arterial pressure in the foot is approximately doubled because of the added pressure exerted by the column of blood extending from the foot to the arch of the aorta. If the foot is emptied of its venous blood by external pressure, the increased pressure head is unopposed by residual blood in the foot and by the hydrostatic venous pressure provided the venous valves are competent.

The present study has shown the following:

Motionless standing increased the blood flow in the foot two to four times above the recumbent level. The large increase in arterial pressure

was not sufficient to dilate maximally the vessels which still retained their tone but apparently sufficient to force more blood through these vessels than could be accounted for by a simple increase in pressure with no increase in vessel size. The blood flow in the erect position at a temperature of 32°c. was only one-fourth as large as when the vessels were maximally dilated by a temperature of 45°c. The blood flow erect at 32°c. was approximately equal to the blood flow supine at 45°c. Blood flow supine in the foot emptied of its venous blood was about 50 per cent greater than in the non-emptied foot.

These observations suggest that a properly timed peripheral venous pump rhythmically emptying the foot of its venous blood would cause at least a 100 per cent increase in the blood flow of the erect subject above that present in the same subject recumbent. The actual value of this procedure in the treatment of peripheral vascular disease remains to be evaluated.

Direct Action of Hypoxia upon the Vasomotor Center

Theodore G. Bernthal, m.d. (*introduced by Paul F. Hahn, M.D.*)

From the Department of Physiology, Medical College of South Carolina, Charleston, S. C.

The responses of the vasomotor center (anesthetized dogs) to hypoxia were recorded during the absence of all known chemoreceptor support. Responses of the vasomotor center were indicated by changes in arterial blood volume flow in the foreleg. The vascular bed of the foreleg was protected from hypoxia and local hemodynamic conditions were maintained constant. Thus, changes in leg blood flow during hypoxia could result only from altered activity of the vasomotor center.

In four of eleven animals, reduction of the oxygen tension of inspired air to 0–52 mm. Hg caused only diminished leg blood flow, indicating predominance of excitatory action of hypoxia at the vasoconstrictor center. In six animals the responses were mixed, vasoconstriction occurred during some intensities of hypoxia or at some stage of single responses, vasodilatation at others. In one animal only vasodilatation occurred.

The results suggest two separate but simultaneous effects of hypoxia on the vasoconstrictor center, one depressant and one excitatory, with a varying balance between them. In general, responses in which excitation dominated were the more frequently encountered. A corollary conclusion is that the arterial hypotension commonly exhibited during hypoxia by chemoceptively deafferented animals is not dependent upon depression of the vasoconstrictor center.

Some Clinical Experiences with Members of the Vitamin M Group (Pteroylglutamic Acid, Fermentation Factor and Pteroic Acid)

Edgar Jones, m.d. (*by invitation*), Henry F. Warden, m.d. (*by invitation*) *and* William J. Darby, m.d.

From the Departments of Medicine and Biochemistry, Vanderbilt University School of Medicine, Nashville, Tenn.

Pteroylglutamic acid (PGA) is hemopoietically active when administered orally or parenterally to patients with sprue, pernicious anemia or nutritional macrocytic anemia. A comparison of its activity with liver extract indicates that orally administered PGA results in reticulocyte maxima equally as high as does liver extract. The subsequent erythrocyte regeneration is satisfactory. Eight patients who had been treated in a previous relapse with liver extract responded with equally good or higher erythrocyte levels when treated in a subsequent relapse with 5 to 15 mg. of PGA daily.

In sprue PGA can favorably influence the gastrointestinal malabsorption as reflected by the return toward normal of glucose tolerance, stool fat content, vitamin A tolerance, serum carotene and plasma tocopherol. The gastrointestinal picture as revealed by x-ray has reverted to normal in one patient under constant therapy with PGA. The effect of PGA on the neurologic defects in pernicious anemia remains to be clarified.

A case of sprue has exhibited a reticulocytosis of 38 per cent accompanied by clinical and hematologic improvement following daily parenteral administration of 10 mg. doses of "fermentation factor" (pteroyltriglutamic acid). A patient with pernicious anemia in relapse failed to respond significantly to the oral administration of 7.0 mg. daily of pteroic acid but subsequently responded to the oral administration of 5 mg. of PGA daily.

Urea Synthesis in the Nephrectomized Rat. A Method for the Study of Rapid Changes in Protein Metabolism

Frank L. Engel, M.D., E. Irene Pentz, M.D. (*by invitation*) *and* Mildred G. Engel, M.D. (*by invitation*)

From the Department of Medicine, Emory University School of Medicine, Atlanta, Ga.

There has been increasing interest during recent years in the relation of illness, injury and various endocrines to nitrogen metabolism. Much has been learned about overall nitrogen balance but there are many gaps in our knowledge of the protein metabolism and the exact time relationship between various types of stimuli and the responses in acceleration or inhibition of protein catabolism.

The present report presents an improved method for the study of rapid changes in protein metabolism in rats by which one is enabled to detect changes in three hours or less with a high degree of accuracy. It is based on the measurement of urea nitrogen accumulation in nephrectomized rats. Its validity depends on (1) the availability of an accurate and sensitive method for the determination of blood urea, (2) the equal distribution of urea throughout the total body water, (3) experimental periods short enough so that significant changes in body water composition are unlikely and (4) a relatively constant rate of rise of blood urea nitrogen during a reasonable period after nephrectomy. These criteria have been met. Data will be presented analyzing the method, and some experiences with the use of various amino acid mixtures, adrenal cortical extract and the effects of hemorrhages and shock will be considered.

Plasma Proteins in Control and Injured Dogs, Goats and Rats

Alfred Chanutin, M.D.

From the Biochemical Laboratory, University of Virginia, Charlottesville, Va.

(This work was done under contract with the Medical Division, C.W.S.)

This laboratory has been engaged in the fractionation of serum of control and injured animals. The serum and fractions have been studied by electrophoretic and chemical procedures.

The serum of dogs injured by mustard, heat, cold or turpentine injections showed increases in alpha and beta globulins and a decrease in albumin concentrations. Fractions isolated from these sera were not present in the serum of control animals and some were characterized by a high lipide content.

The electrophoretic changes in the serum of goats injured by mustard or turpentine were characterized by an increase in the beta globulins and a decrease in albumin concentrations. No increase in lipoproteins was demonstrated in the goat. Four electrophoretically pure proteins have been isolated.

The proteins of whole plasma of rats showed comparatively little change electrophoretically until they were separated into four fractions. After injury, marked increases were noted in the alpha and beta globulins and a decrease in albumin concentrations.

Urine Volume and Urinary Sodium Excretion during Water Diuresis

A. J. Crutchfield, M.D. (*by invitation*) *and* J. Edwin Wood, Jr., M.D.

From the Department of Medicine, University of Virginia Medical School, Charlottesville, Va.

The influence of water diuresis on urinary sodium excretion has been observed in normal individuals and patients with congestive heart failure. Hourly total renal excretion of sodium and urine has been determined for six consecutive hours following the ingestion of one liter of water. This pattern of sodium and water excretion was studied following: (1) plain water and (2) plain water plus certain diuretic substances, appropriately preceded in each case by plain water controls. Sodium determinations were made by the photometric method, the accuracy of which has been discussed in a previously submitted summary. Altogether eighty-six experiments have been done on forty patients.

From these experiments a definite pattern of sodium and water excretion has been recorded. This pattern is essentially the same in outline for both normal and congestive heart failure patients, though quantitatively different.

Mercupurine and intravenous aminophyllin regularly produced a disproportionate increase

in urine volume and total urinary sodium in favor of the latter. This suggests that the primary renal action of these substances may be depression of tubular reabsorption of sodium. Xanthines by mouth have a similar, though much less powerful effect. Urea and glucose under the conditions of this experiment produced no significant effect on urine volume or sodium excretion.

From these observations it would appear that water diuresis does not increase urinary sodium elimination but may actually depress it.

Fluorescent Tracer Substances in the Determination of Circulation Times in Man

William Adolph, M.D., Travis Winsor, M.D., Walter C. Ralston, M.D. *and* George M. Leiby, M.D. (*introduced by George E. Burch, M.D.*)

From the Medical Division, Birmingham General Hospital, Van Nuys, Calif.

The purpose of the present presentation is (1) to demonstrate the use of riboflavin as a fluorescent tracer substance, (2) to present a technic which renders circulation time of greater clinical value and (3) to demonstrate the value of measurements in various segments of the cardiovascular system. The technic was to raise a histamine wheal on various portions of the body. After approximately one minute riboflavin was injected into the antecubital vein. The time was measured from the beginning of the injection to the appearance of yellow-green fluorescence in the periphery of the wheal detected using filtered ultraviolet light. Normal individuals and patients with congestive failure were studied. A number of fluorescent materials were studied *in vivo* and *in vitro*. Riboflavin and fluorescein were the most innocuous, were readily diffusible in tissue spaces and easily visible giving sharp end points in a darkened room. Peak fluorescence for riboflavin occurred in dilutions ten times greater than for fluorescein. Maximum fluorescence was more intense with fluorescein. Optimum dose for riboflavin *in vivo* was 0.8 mg. per kilo. Arm to arm times were determined among normal individuals using riboflavin and fluorescein. Both substances gave comparable results (range fourteen to twenty-six seconds, average 19). Riboflavin circulation times varied with age, the shortest normal arm to arm time being six seconds in an infant. Circulation times were determined over short (arm to arm) and long (arm to foot) segments of the vascular tree among normal individuals and those with congestive failure. Times obtained from long segments were a more sensitive index of circulatory retardation than times obtained over shorter segments. Circulation times through a systemic arterial segment was determined by taking the difference between arm to arm and arm to foot times. In some instances the segment time was abnormal (greater than twelve seconds under standard conditions) in patients with failure when the arm to arm time was normal.

Observations on Abdominal Visceral Pain Pathways in Patients Undergoing Celiac Ganglionectomy and Vagotomy or Sympathectomy

Keith S. Grimson, M.D.

From the Department of Surgery, Duke University School of Medicine, Durham, N. C.

Celiac ganglionectomy alone has been performed during the course of exploratory laparotomy in four patients with so-called biliary dyskinesia. Another had right splanchnicectomy only. Celiac gangionectomy was employed for pain from recurring pancreatitis in one patient. Celiac ganglionectomy and subdiaphragmatic vagotomy were performed in two patients with severe functional abdominal pain. Observations concerning the effect of these operations and also concerning visceral pain after transthoracic vagotomy for peptic ulcer and after splanchnicectomy during sympathectomy for hypertension will be presented.

It is concluded that the vagus nerves do not carry visceral afferent pain pathways and that the splanchnic nerves do. A major portion of the splanchnic visceral afferent pain pathways travel through the celiac ganglia.

CONDITION	CONDITION	CONDITION
Various dyspepsias of chronic gallbladder disease.	Noncalculous cholecystitis; gallstone patients (poor surgical risks); cholelithiasis without previous colic.	Biliary constipation.
THERAPY	**THERAPY**	**THERAPY**
Unconjugated ketocholanic acids (Ketochol), antispasmodics, generous diet of uncooked fats.	Ketochol, bland diet with uncooked fats, antispasmodics.	Ketochol.
RESULTS	**RESULTS**	**RESULTS**
46.5% complete relief, 46.5% partial relief, 7.9% no relief.	Satisfactory response to the medical regimen.	Prompt return of stools to normal size, immediate subsidence of other distressing symptoms.
AUTHOR	**AUTHOR**	**AUTHOR**
DeLor, C. J.; Means, J. W.; Shinowara, G. J., and Reinhart, H. L.: Rev. Gastroenterol. *8*:48 (Jan.-Feb.) 1941.	Dolkart, R. E.: Illinois M. J. *87*:43 (Jan.) 1945.	Gauss, H.: Am. J. Digest. Dis. *12*:224 (July) 1945.

KETOCHOL: *Efficient hydrocholeretic*

PAVATRINE: *Smooth muscle antispasmodic*

Ketochol and Pavatrine are the registered trademarks of G. D. Searle & Co., Chicago 80, Illinois

---

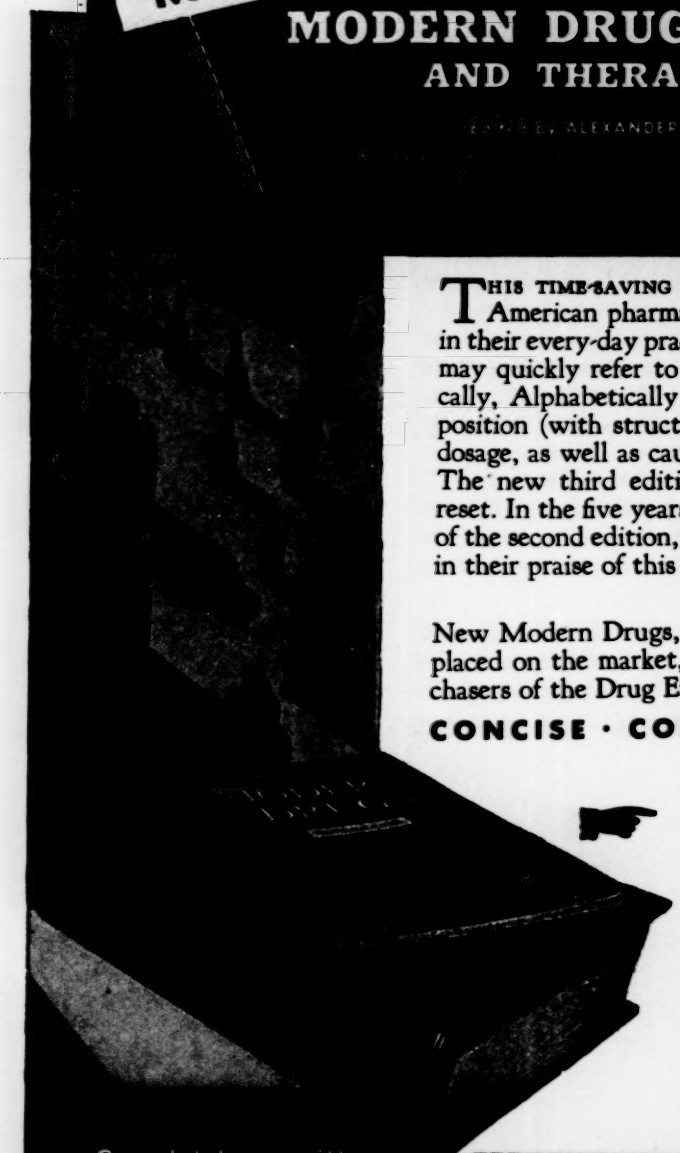
SEARLE *Research in the Service of Medicine*

NOW READY

The New, Completely Rewritten, 3rd Edition

MODERN DRUG ENCYCLOPEDIA
AND THERAPEUTIC INDEX

Edited by ALEXANDER E. GUTMAN, M.D., F.A.C.P.



THIS TIME-SAVING volume presents 8140 Ethical drugs of American pharmaceutical manufacturers that doctors use in their every-day practice. With this service on your desk, you may quickly refer to any medicinal preparation Therapeutically, Alphabetically or by Manufacturer, and find its composition (with structural formulas), action, uses, supply and dosage, as well as cautions and contraindications.

The new third edition has been completely rewritten and reset. In the five years that have elapsed since the publication of the second edition, purchasers everywhere have been lavish in their praise of this service.

KEPT UP TO DATE

New Modern Drugs, which completely describes new drugs placed on the market, is issued quarterly and is sent to purchasers of the Drug Encyclopedia at no extra charge.

CONCISE · COMPLETE · AUTHORITATIVE

Invaluable!

Your book is invaluable and unique—indispensable, in fact, to me.

This book has saved us a lot of time, given us much valuable knowledge. We will always buy the new one. Keep it high type. That's your market.

Splendid!

This is a splendid service, I could not get along without it.

Circulars and catalogs are mislaid. Not so, if in a book. The book makes a grand reference. I refer to it every day. It is my bible. I am in love with the book.

Approximately 1200 pages

Completely rewritten
and reset
handsomely bound
Size 2 x 6 x 9
Price postage prepaid $10.00

NEW MODERN DRUGS
49 W. 45th St. New York 19, N. Y.

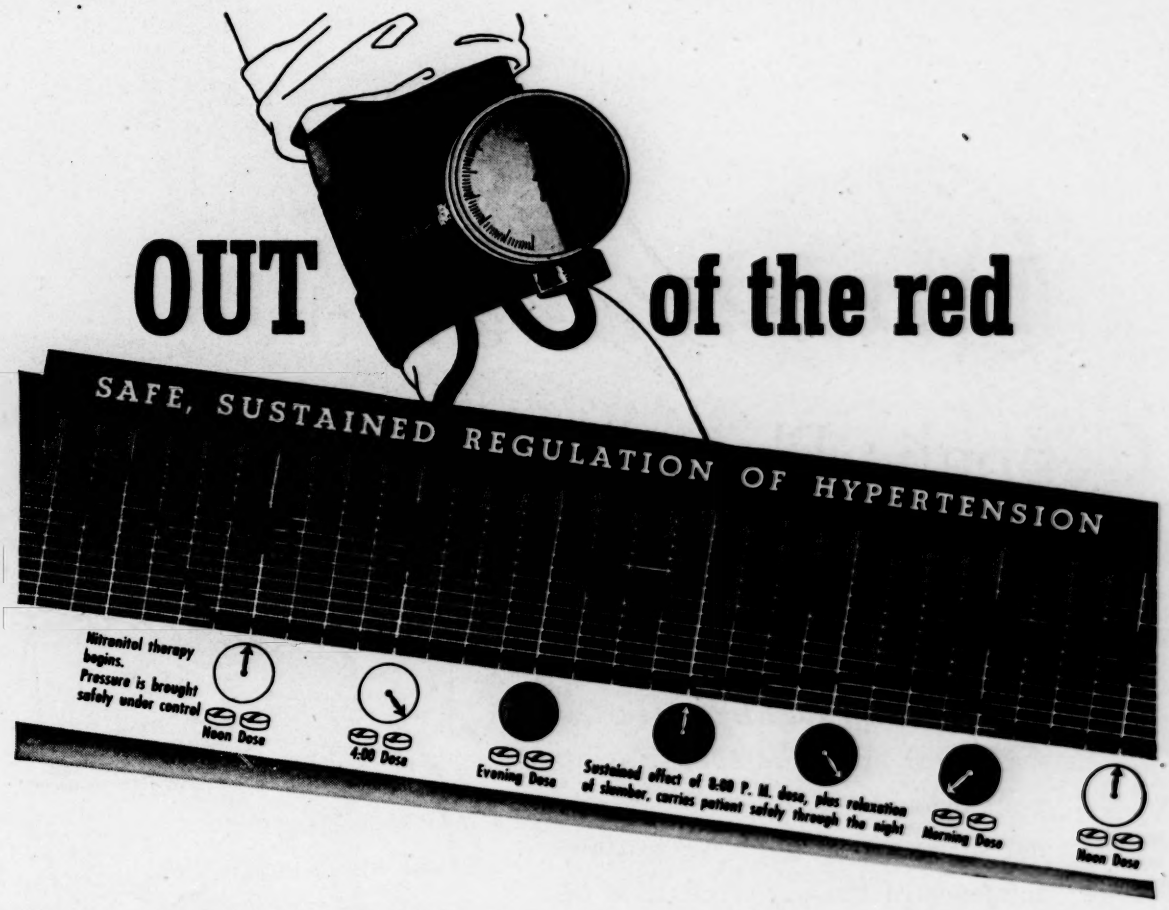
NEW MODERN DRUGS 49 W. 45th St., New York 19, N. Y.

Enclosed is the sum of ten dollars ($10.00) for which please send me postpaid GUTMAN'S MODERN DRUG ENCYCLOPEDIA AND THERAPEUTIC INDEX AND NEW MODERN DRUGS. (Remittance must accompany order.)

NAME .....

ADDRESS .....

CITY AND ZONE ..... STATE .....



Vasorelaxation produced by Nitranitol is GRADUAL, avoiding the dangerously abrupt blood pressure fluctuations of the quick-acting drugs.

The hypotensive effect of Nitranitol is PROLONGED, each dose overlapping the one before—permitting maintenance of a relatively constant pressure.

The negligible clinical toxicity of Nitranitol, making it SAFE for use over an indefinite period, is in contrast to the cumulative toxicity of the thiocyanates.

Gradual, Prolonged, Safe Vasodilation with

NITRANITOL

T. M. REG. U. S. PAT. OFF.

Nitranitol contains ½ gr. mannitol hexanitrate in each scored tablet. Dosage is 1 to 2 tablets every four hours. Available in hospital and prescription pharmacies in bottles of 100 and 1000.

For cases requiring sedation in addition to vasodilation.
NITRANITOL WITH PHENOBARBITAL
Each scored tablet contains ½ gr. mannitol hexanitrate and ¼ gr. phenobarbital. Bottles of 100 and 1000.

MERRELL

THE WM. S. MERRELL COMPANY
CINCINNATI, U. S. A.

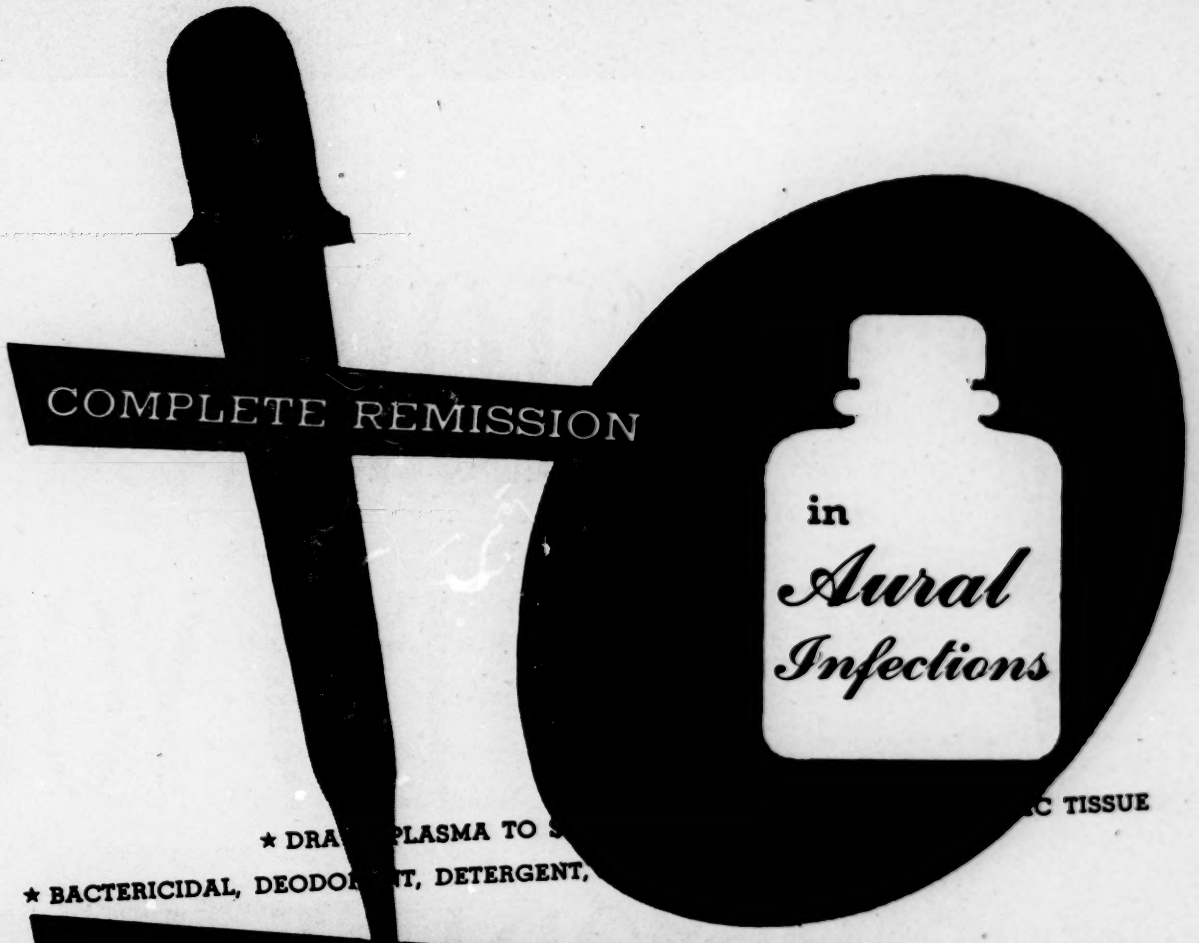
Candy and the Cephalic Phase of Digestion

That the pleasant sense of satiety and satisfaction which follows a good meal is conducive to trouble-free digestion has been repeatedly experienced by everyone. The psychic influence of the sight and taste of attractive food upon the secretion of the digestive juices and upon gastrointestinal motility is probably the basis for this observation. A meal which ends with a piece or two of candy is usually regarded as a satisfying meal. In this manner candy can rob even an ordinary meal of its drabness. Children look forward to this treat at the end of their meals; this very anticipation encourages them to eat their other foods more eagerly. And few indeed are the adults who do not enjoy a sweet after lunch or dinner.

Candies are made with many wholesome and nutritionally valuable foods—milk, butter, eggs, fruits, and nuts. To the extent these foods are present, candies provide valuable protein, minerals, and B complex vitamins. Readily utilized caloric food energy is also supplied by candies.

COUNCIL ON CANDY OF THE NATIONAL CONFECTIONERS ASSOCIATION

1 NORTH LA SALLE STREET • CHICAGO 2, ILLINOIS



Glycerite of Hydrogen Peroxide *plus*
With Carbamide

★ **BIBLIOGRAPHY**

Arch. Otolaryngol., 43:605, 1946.
E., E., N., & T. Mo., 26:27, 1947.
Laryngoscope, 56:556, 1946.
New Eng. J. Med., 234:468, 1946.
Annals of Allergy, 4:33, 1946.
J. A. Ph., A., (Sc. Ed.) 35:304, 1946.

Literature on request.

Clinical studies concerned with the use of Glycerite of Hydrogen Peroxide in the treatment of chronic purulent otitis media demonstrated seventeen of twenty-nine patients in complete remission in 14 days and the remainder by the 38th day. The patients studied presented conditions existent for periods of 2 weeks to over 40 years. Previous treatment by the usual therapeutic means, including tyrothricin or penicillin, was ineffective in all cases.

Constituents:

Hydrogen Peroxide 1.446%, Urea (Carbamide) 2.554%, 8-Hydroxyquinoline 0.1%.
Dissolved and stabilized in substantially anhydrous glycerol . . . q.s. ad. 30cc.

Available on prescription in one-ounce bottle with dropper.
Administration: One-half dropperful two to four times daily.

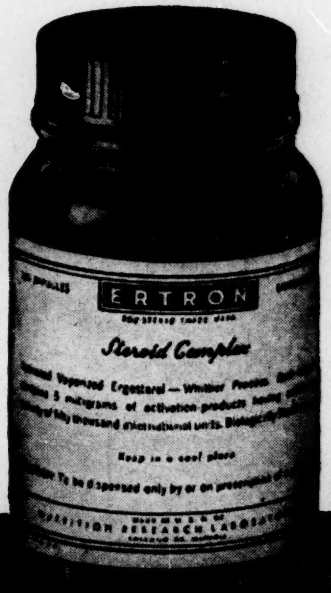
International **PHARMACEUTICAL CORPORATION**
132 NEWBURY STREET, BOSTON 16, MASSACHUSETTS

DOCTOR, WHAT DO YOU PRESCRIBE FOR ARTHRITIS?

ERTRON*

Steroid Complex, Whittier

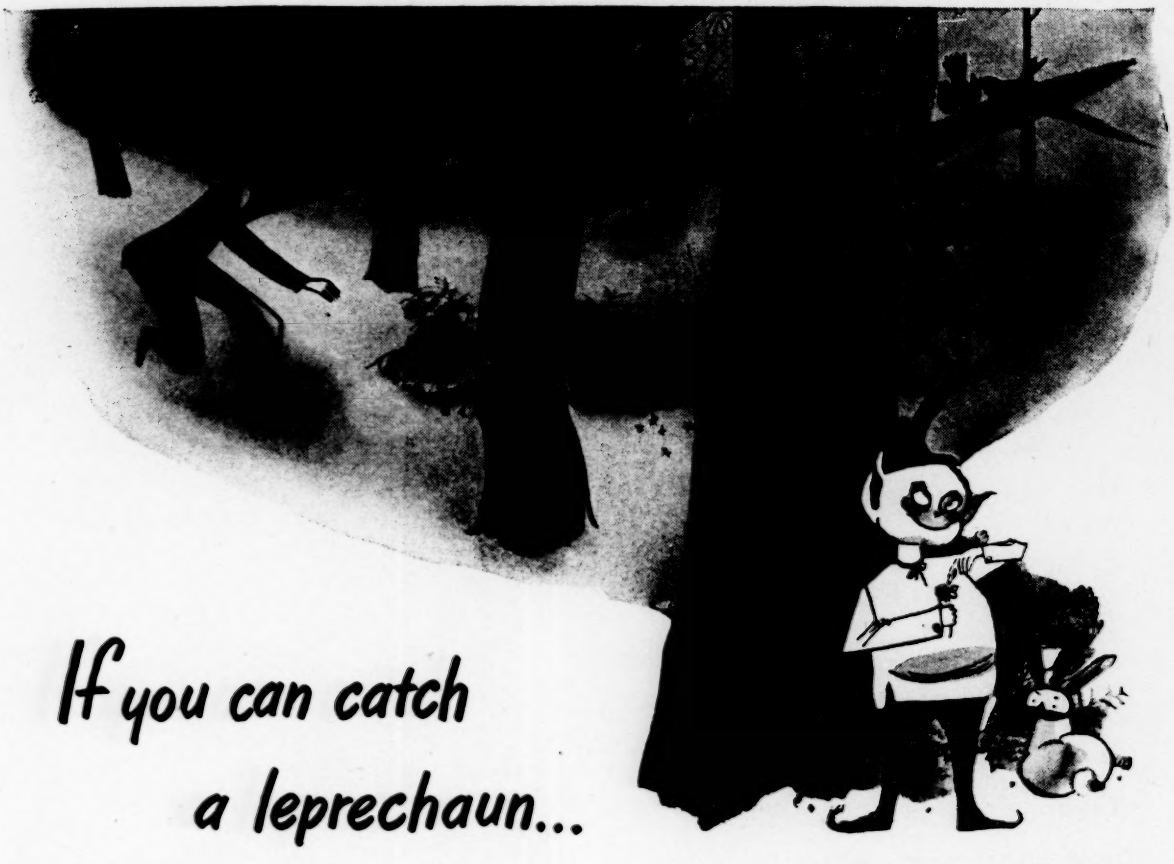
There was a time when Arthritis could be considered hopeless. Today, as the literature shows, the gains made by Ertron over the dread disease have been outstanding. Ertron is the most widely prescribed anti-arthritic today.



*Reg. U. S. Patent Office

NUTRITION RESEARCH LABORATORIES

CHICAGO



If you can catch a leprechaun...

A leprechaun, according to Irish legend, is a dwarf who keeps a pot of gold hidden away.

If you can catch a leprechaun, your troubles are over.

Because he keeps his gold just for ransom money. If you catch him, he'll quickly tell you where his gold is, so you'll let him go.

The best place to look for a leprechaun is in the woods. They're green, and only about nine inches tall, so you'll have to—

Or maybe you don't believe in leprechauns.

Maybe it would be more practical to just keep working for your money. But you can learn one good lesson from these little fellows.

A small pot of gold put to one side is a great help when trouble catches *you*.

And there's a much faster and easier way to get your pot of gold than by catching leprechauns.

You can buy U. S. Savings Bonds through an *automatic* purchase plan.

If you're employed you can sign up for the Payroll Savings Plan. If you have a bank account you can sign up for the Bond-A-Month Plan.

Either way, your pot of gold just saves itself, painlessly and automatically.

And your money increases one third every ten years. That would make a leprechaun turn even greener with envy.

Save the easy, automatic way—with U.S. Savings Bonds

Contributed by this magazine in co-operation with the Magazine Publishers of America as a public service.

WHENEVER THE NUTRITIONAL STATE MUST BE IMPROVED

The food drink made by mixing Ovaltine with milk finds frequent application whenever underpar nutrition is encountered. It is equally valuable whether the need for dietary supplementation arises from the ravages of acute infectious disease, from dietary limitations made necessary by surgery, or from faulty food selection over a prolonged period.

This nutritional supplement is delicious in taste, readily digested, and thoroughly bland. It may be taken either hot or cold, as the patient desires, and is appealing to both children and adults. It supplies a wealth of virtually all essential nutrients including ascorbic acid and B complex and other vitamins. Its proteins are biologically complete, a feature of importance in the correction of debility states. Three glassfuls of this delicious food drink daily round out even an average diet to full nutritional adequacy.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.

Ovaltine

Three servings daily of Ovaltine, each made of ½ oz. of Ovaltine and 8 oz. of whole milk,* provide:

CALORIES	669	VITAMIN A	3000 I.U.
PROTEIN	32.1 Gm.	VITAMIN B_1	1.16 mg.
FAT	31.5 Gm.	RIBOFLAVIN	2.00 mg.
CARBOHYDRATE	64.8 Gm.	NIACIN	6.8 mg.
CALCIUM	1.12 Gm.	VITAMIN C	30.0 mg.
PHOSPHORUS	0.94 Gm.	VITAMIN D	417 I.U.
IRON	12.0 mg.	COPPER	0.50 mg.

*Based on average reported values for milk.

YOUR YEARLY SUBSCRIPTION TO

The American Journal of Medicine

BRINGS YOU

"Today's Medicine for Tomorrow's Use"

24 Conferences

2 Symposia

2 Seminars

3 Research Society Reports

100 Clinical Articles

•

1536 Text Pages Yearly

Profusely Illustrated

•

THE YORKE PUBLISHING CO., INC.

also publishers The American Journal of Surgery

Established July 1946

EDITORIAL BOARD

EDITOR

ALEXANDER B. GUTMAN, M.D.
Assistant Professor of Medicine, Columbia University, College of Physicians and Surgeons, New York

ADVISORY BOARD

WALTER W. PALMER, M.D., *Chairman*
Bard Professor Emeritus of Medicine, Columbia University, College of Physicians and Surgeons, New York
DAVID P. BARR, M.D.
Professor of Medicine, Cornell University Medical College, New York
FRANCIS G. BLAKE, M.D.
Sterling Professor of Medicine, Yale University of Medicine, New Haven
ARTHUR L. BLOOMFIELD, M.D.
Professor of Medicine, School of Medicine, Stanford University, San Francisco
EUGENE A. STEAD, JR., M.D.
Professor of Medicine, School of Medicine, Duke University, Durham
JOSEPH T. WEARN, M.D.
Professor of Medicine, School of Medicine, Western Reserve University, Cleveland

ASSOCIATE EDITORS

HERRMAN L. BLUMGART, M.D., Boston
HARRY GOLD, M.D., New York
A. McGEHEE HARVEY, M.D., Baltimore
GEORGE H. HOUCK, M.D., San Francisco
CHESTER S. KEEFER, M.D., Boston
T. GRIER MILLER, M.D., Philadelphia
WALTER L. PALMER, M.D., Chicago
OSWALD H. ROBERTSON, M.D., Chicago
EPHRAIM SHORR, M.D., New York
GEORGE W. THORNE, M.D., Boston
WILLIAM S. TILLETT, M.D., New York
ROY H. TURNER, M.D., New Orleans
RUSSELL M. WILDER, M.D., Rochester, Minn.
M. M. WINTROBE, M.D., Salt Lake City
W. BARRY WOOD, M.D., St. Louis
JOHN B. YOUMANS, M.D., Chicago

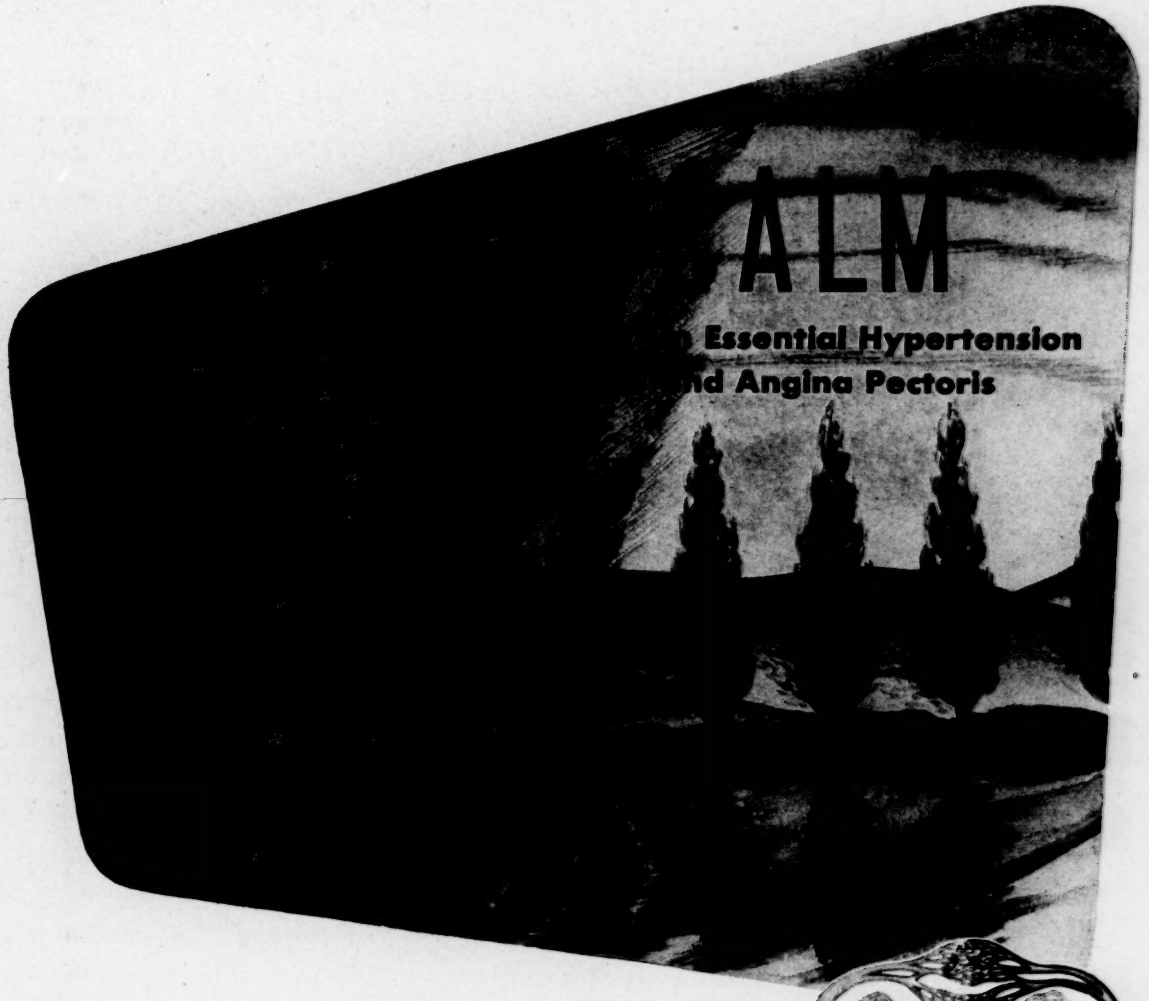
SUBSCRIPTION ORDER FORM

THE AMERICAN JOURNAL OF MEDICINE
49 WEST 45TH STREET, NEW YORK 19, N. Y.

Please enter my subscription to the new monthly journal, THE AMERICAN JOURNAL OF MEDICINE. Subscription U.S.A. $10.00 per year. $12.00 Foreign.

NAME_____ ADDRESS_____

CITY_____ STATE_____



MAXITATE

REG. U.S. PAT. OFF.

MANNITOL HEXANITRATE, STRASENBURGH

The Original Stabilized Formula

Pioneered by STRASENBURGH *Research*

Gradual **and** ***prolonged*** **vasodilation... lasting 5 to 6 hours. Uniformly dependable action.**

PACKAGE DATA:

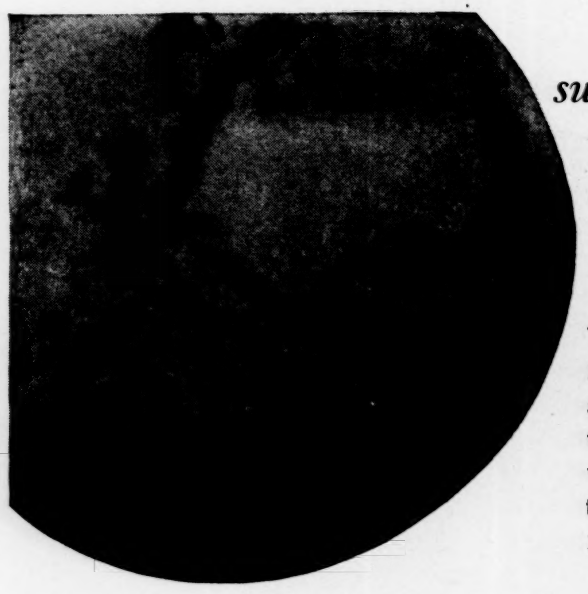
Available in bottles of 100 and 1000 tablets.

Maxitate ¼ gr. (white) Not Scored
Maxitate ½ gr. (white) Scored
Maxitate ½ gr. with Phenobarbital ¼ gr. (blue) Scored
Maxitate ½ gr. with Phenobarbital ½ gr. (pink) Scored
Maxitate ½ gr. with Nitroglycerin 1/100 gr. (violet) Scored

R. J. STRASENBURGH Co.

PHARMACEUTICAL CHEMISTS SINCE 1886

ROCHESTER 4, NEW YORK



Photomicrograph of DIPLOCOCCUS PNEUMONIAE (magnified 1,350 times), after "typing" with homologous antiserum by Neufeld method. The swollen, unstained, sharply outlined capsules contain the type-specific polysaccharide, which is mixed with similar antigens from other types of pneumococci in the preparation of Solution of Pneumococcus Polysaccharides.

successful active type-specific immunization against pneumococcal pneumonia

"The evidence . . . demonstrates clearly that immunization of man with the specific capsular polysaccharides of pneumococcus types I, II, V, and VII is effective in preventing the development of pneumonia due to these types in the immunized subjects."[1]

1. MacLeod, C. M.; Hodges, R. G.; Heidelberger, M., and Bernhard, W. G.: J. Exp. Med. *82*:445 (Dec. 1) 1945.

In the above mentioned investigation on 17,035 subjects with a preparation made by Squibb, pneumonia of the types represented in the vaccine was entirely eliminated in the immunized group (8,586), excepting for four cases which developed before specific immunity had been established. And in the non-immunized group of 8,449 controls, all of whom were closely associated with the immunized group, the incidence of these types of pneumonia was *greatly lowered* through the reduction of "carriers." Reactions were mild. The slight arm soreness reported by those injected lasted only 3 to 4 days.

Solution of

PNEUMOCOCCUS POLYSACCHARIDES

Type-specific

supplied in two combinations of types to which adults and children, respectively, are generally most susceptible:

COMBINATION A: Containing types 1, 2, 3, 5, 7 and 8. (Primarily for adults)

COMBINATION B: Containing types 1, 4, 6, 14, 18 and 19. (Primarily for children)

DOSAGE: A *single* subcutaneous injection of 1 cc. for adults, or children over 12 years of age; 0.5 cc. for children under that age. Immunity usually develops within 6 to 9 days and is effective for at least one year.

AVAILABLE: Each combination supplied in 1 cc. and 5 cc. rubber-stoppered vials.

Professional leaflet, "Active Immunization Against Pneumococcal Pneumonia" is available upon request.

SQUIBB MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858